Lab on a Chip

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Point-of-Care Diagnostics: Recent Developments in a Pandemic Age

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Abstract

In this review, we provide an overview of developments in point-of-care (POC) diagnostics during the COVID-19 pandemic. We review these advances within the framework of a holistic POC ecosystem, focusing on points of interest – both technological and non-technological – to POC researchers and test developers. Technologically, we review design choices in assay chemistry, microfluidics, and instrumentation towards nucleic acid and protein detection for severe acute respiratory coronavirus 2 (SARS-CoV-2), and away from the lab bench, developments that supported the unprecedented rapid development, scale up, and deployment of POC devices. We describe common features in the POC technologies that obtained Emergency Use Authorization (EUA) for nucleic acid, antigen, and antibody tests, and how these tests fit into four distinct POC use cases. We conclude with implications for future pandemics, infectious disease monitoring, and digital health.

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Main Text

1. Introduction

In January 2020, within two weeks of the publication of the genome sequence of SARS-CoV-2, the first reverse transcription polymerase chain reaction (RT-PCR) diagnostic test to detect the virus was developed.[1] During the beginning stages of the pandemic, countries with high rates of testing had low transmission rates as testing helped identify patients to isolate and prevent the spread of the virus.[1] To meet the tremendous demand for diagnostics, laboratory-based high-throughput testing was scaled up, but faced limitations in supply and in bringing subjects to dense environments.

An effort to develop and deploy POC diagnostics ensued, aided by large government and private sector investments as well as revised regulatory guidelines. Here, we review developments in POC diagnostics during the COVID-19 pandemic, using a framework we presented in 2017 which highlighted the synthesis of microfluidic and smart connected devices towards decentralized testing.[2] This "POC ecosystem" (**Figure 1**) consists of technological and non-technological components. Technologically, advances were made across disciplines, covering assay chemistry, microfluidics, instrumentation, and data analytics. Away from technology, the pandemic escalated awareness in government, media, and consumers in comprehensive testing and surveillance, increased understanding of different types of diagnostics, and created pathways to implementation; we summarize these non-technological developments (with a focus on the United States) as clinical workflow, regulatory guidance, reimbursement, and legislation. Synthesis of technological and non-technological considerations led to targeted solutions towards SARS-CoV-2 testing that were developed with unprecedented speed. The review focuses on nucleic acid, antigen, and antibody tests, but we also provide an

overview of selected novel POC diagnostic technologies, such as face masks, breathalyzers and T-cell testing. We analyzed POC tests that obtained FDA EUA for SARS-CoV-2 (as of June 2021), describe common features in the companies that developed these tests, and provide commercial case studies for selected technologies. We then group SARS-CoV-2 tests into the four distinct POC use cases, and for each case, discuss the technological bases of the tests as well as overall testing trends. Finally, we discuss implications for monitoring of future infectious disease as well as for digital health more broadly.

2. The POC Ecosystem for SARS-CoV-2 Diagnostics

In this section, we describe how the POC ecosystem has developed during the COVID-19 pandemic. The POC ecosystem contains both technology and non-technology components (**Figure 1**).[2] Technologically, the needs for speed, low-cost, and simplicity were reinforced, accelerating the trend for miniaturized connected diagnostics for decentralized settings.[2,3] For each type of SARS-CoV-2 diagnostic assay (nucleic acid, antigen, and antibody tests), we highlight key advances in assay chemistry, microfluidics, and instrumentation, and select three commercial POC tests as illustrative examples. In addition to the three assay types, we provide an overview of selected emerging technologies as well as discuss developments in data analytics across POC devices.

In the deployment of POC diagnostic tests, remarkable developments have taken place in clinical workflow, regulatory guidance, reimbursement, and legislation. We review these developments and their interplay with technological advances, and analyze common features of companies that successfully obtained EUA for POC SARS-CoV-2 diagnostic devices.

2.1 Core Technology Components

2.1.1 Nucleic Acid Tests

Nucleic acid tests, or molecular diagnostic tests, detect RNA from SARS-CoV-2, a single-stranded RNA virus.[4,5] A number of techniques to amplify and detect viral RNA were developed and deployed, although the gold standard method for RNA detection remains to be RT-PCR.[5–7]

Assay Chemistry

A number of amplification, detection, and readout methods have been developed[8] as an alternative to PCR. Isothermal amplification techniques, where a single temperature requirement can simplify requirements for a POC molecular test,[9,10] include loop-mediated isothermal amplification (LAMP), recombinase polymerase amplification (RPA), and rolling circle amplification (RCA).[11] LAMP is one of the most mature and widely studied isothermal amplification methods[12]; it uses 2 to 3 primer sets and a strand-displacing polymerase to facilitate exponential amplification of the target at a single temperature of ~60-65 ℃.[13] Several commercial entities that have obtained EUA for SARS-CoV-2 detection use LAMP (**Table 1**), with many studies reporting comparable performance to RT-PCR.[14–16] Another isothermal method, nicking enzyme amplification reaction (NEAR),[17] was used in the Abbott ID NOW system and was one of the first POC methods made available during the pandemic.[18] As field evaluations of the Abbott ID NOW have reported lower sensitivities than the initial results reported by the manufacturer, more independent real-world evaluations of a wide range of POC tests – including isothermal amplification and CRISPR tests – will be beneficial towards an objective understanding of the field performance of these technologies.[19]

Isothermal amplification methods have been paired with CRISPR technology to create a new class of molecular diagnostics. For example, Cas12 and Cas13 enzymes are used with CRISPR RNA (crRNA) to target a specific nucleic acid sequence complementary to the cRNA. While Cas12 detects ssDNA, and Cas13 detects ssRNA, both enzymes have collateral cleavage activity that cleaves any nucleic acids in their vicinity indiscriminately after recognition.[8] A commercial assay for SARS-CoV-2 detection has been developed by Mammoth Biosciences with the DNA Endonuclease Targeted CRISPR Trans Reporter (DETECTR) platform using RT-LAMP and Cas12.[20–22] Another company, Sherlock Biosciences, uses Cas 13 and RT-LAMP for their SHERLOCK (specific high-sensitivity enzymatic reporter unlocking) platform.[23,24] While the EUA assays for Mammoth and Sherlock measure fluorescence generated upon cleavage of a reporter molecule and are restricted to laboratory settings,[22,23] both companies have also demonstrated a visual detection method with a lateral flow assay.[20,25] However, these methods still require a number of sample processing steps (including pre-amplification) so both companies have announced industry partnerships to translate the technology towards POC use.[26,27] It is worth noting that Sherlock Biosciences has also demonstrated advances in simplifying sample preparation with CRISPR,[25,28], and is working on a separate platform termed INSPECTR (Internal Splint-Pairing Expression Cassette Translation Reaction) that utilizes cell-free, synthetic translation as a biosensor.[29–31] Current research efforts in the field are focused on translating CRISPR technology to a POC use.[3,32–35] Some demonstrations include a minimally instrumented SHERLOCK test,[36] amplification free detection in a microfluidic chip[37] and lateral flow strip[37], and a multiplexed lab-on-paper platform.[38]

PCR is still the gold standard in molecular diagnostics. AuNPs can be added to the reaction mix to support plasmonic thermocycling, where infrared radiation rapidly generates heat

from localized surface plasmon resonance of the nanoparticles. This technology was previously demonstrated to produce rapid thermocycling,[39–42] and is being adapted for POC use for COVID-19[42] (including in our lab, for saliva samples without extraction, unpublished results).

For signal detection, PCR has used fluorescent dyes like SYBR Green for non-specific detection, or Taq man probes for specific detection. As an alternative to fluorescence, some developers have turned to colorimetric readouts. For example, the Mesa Biotech Accula platform for SARS-CoV-2 uses a LFA to detect PCR products, and a visual band is created to generate a test result.[43] The Visby Medical platform uses capture reagents in a "flow cell" along with an enzymatic reaction (using horseradish peroxidase) to generate a visual spot.[44] While visual readouts of PCR or nucleic acid amplification products with capture reagents on substrates (e.g., paper, plastic) has been demonstrated in previous research,[45–47] the pandemic has spurred further demonstrations for non-instrumented readout methods.[48,49] Another company, Lucira Health, skips the LFA and uses a simple colorimetric readout with a pH-sensing molecule, a method other RT-LAMP assays have employed for detection of SARS-CoV-2 as well.[15,50,51] With these simple visual readouts aided by novel assay chemistry, novel forms of nucleic acid testing are being designed for decentralized use.

Microfluidics

Nucleic acid detection involves three critical steps: 1) sample preparation, 2) amplification, 3) detection. Given the number of steps involved, assay integration has always been critical for the development of POC molecular tests. With an emphasis on decentralized diagnostics during the pandemic, assay integration became even more important in order to create simple-to-use tests that are accessible to various end users and can be conducted outside traditional laboratory settings.[52] Indeed, many POC SARS-CoV-2 diagnostics that have been

developed incorporate innovations in microfluidics (**Table 1)**, both traditional microfluidic and paper-based assays.[53,54] We describe some of these innovations below, with a focus on simplifying sample collection and preparation steps, towards simpler assay integration.

The first RT-PCR test for SARS-CoV-2 (from the CDC) required a nasopharyngeal swab. However, collection of NP swabs requires a trained technician, can be painful to the receiver, and led to a national swab shortage. The massive deployment of COVID-19 testing spurred a significant push towards scalable workflow and instruments. Nasal swabs, which are easier to administer and can be collected by untrained personnel,[55] showed comparable performance to nasopharyngeal swabs, validating their use in times of nasopharyngeal swab shortage.[56] In addition, saliva-based COVID-19 tests were developed rapidly after the onset of pandemic,[57] and subsequently has emerged as a viable specimen with potential advantages such as non-invasive and painless sample collection with comparable performance,[58–60] thus paving the way for potentially increased use of saliva for POC diagnostics in the future.[61,62,] Although there are a number of EUA assays for SARS-CoV-2 detection in saliva, questions remain in terms of standardization of sample collection procedure and variability of results.

Along with sample collection, sample processing methods have also been simplified for SARS-CoV-2 detection. Traditionally, RT-PCR calls for sample lysis to release nucleic acids from cells, and then nucleic acid purification to concentrate and remove any PCR inhibitors and contaminants. At the beginning of the pandemic, a shortage in RNA extraction kits hampered efforts to expand testing,[63,64] so researchers began to implement simpler sample processing techniques, and even remove the extraction step altogether.[65,66] For example, extraction-free methods have been demonstrated with RT-PCR on heat-inactivated or lysed samples (96% sensitivity and 99.8% specificity compared Roche Cobas 6800 analyzer),[67] and with a

colorimetric POC test using RT-LAMP (100% sensitivity and specificity compared to previously tested clinical samples) .[68] Several EUA approved diagnostics have removed the extraction step (**Table 1**), although these tests typically demonstrate a limit of detection (LOD) of an order of magnitude or higher compared to tests with nucleic-acid extraction (**Supplementary Table 1**). However, the relationship to LOD can be complex, and is an interplay among sample preparation, the amplification method employed, and the amplification method's sensitivity to inhibitors present in the sample.

Connected Instrument

Given the complexity of assay procedures required for nucleic acid detection, complex instruments are generally required for operations such as fluid actuation, reagent storage, and fluorescent detection. Recent innovations in electronics have allowed for smaller and cheaper instruments, as well as major developments in how these instruments connect to laboratory information systems, government reporting systems, providers, and patients.

Established POC systems have offloaded connectivity and data processing to a nearby computer. For example, the GeneXpert System and BioFire FilmArray require a separate barcode scanner and computer for test operation and data transmission.[69,70] More recent generations, however, integrate processing power into the reader itself (such as a molecular testing instrument that has a built-in tablet computer).[71] Other systems like the Abbott ID NOW or the Roche Cobas Liat analyzer also have a built-in screen for device operation. While the integration of computational power and assay operations onto one device has made nucleic acid testing instruments more portable and truly sample-to-answer, they are still relatively large benchtop instruments that cost thousands of dollars. The use case, which will be discussed in a later section, for such tests is in laboratory settings with trained personnel.

Increasingly, computational power is being offloaded to the most prevalent computer found in society today, the smartphone.[72] For example, the Cepheid system has been one of the most widely used POC PCR systems for SARS-CoV-2[73]; their GeneXpert Omni system for SARS-CoV-2 test[74] is 9 inches tall and weighs 2.2 pounds, and uses a companion smartphone application for its user interface, which allows the user to scan the test cartridge barcode and view results.[75,76,] Another product for SARS-CoV-2, from Cue Health, uses a portable connected reader which can connect to the user's smartphone via Bluetooth, and transmit results to a custom app that also provides test instructions.[77]

Efforts are also being made to lower the cost of instruments. For example, Mesa Biotech uses a low-cost dock (in the hundreds of dollars instead of thousands) by incorporating resistive heaters and utilizing a lateral flow detection method dependent on visual interpretation by the operator.[43,78] Interestingly, a number of nucleic-acid testing products are now moving towards LFA detection or other formats where the signal can be detected visually or by using a smartphone camera. We will discuss these developments in the following sections for rapid antigen and antibody tests, for which an LFA format is already widely used.

Commercial Case Studies

Here we discuss three commercial POC SARS-CoV-2 nucleic acid tests that highlight novel assay chemistry, microfluidics, or instrumentation (a larger overview of nucleic acid tests is provided in **Table 1** and **Table 2)**. Performance data collected from company EUA documentation is summarized in **Supplementary Table 1.** Emphasizing the push towards POC use and also home use, we discuss user steps and the design of technological elements that enable a streamlined workflow.

Visby Medical's COVID-19 Point of Care Test is a handheld, fully disposable and automated RT-PCR device that detects the SARS-CoV-2 N gene and is currently authorized for POC use (**Figure 2C**). Under the supervision of a healthcare provider, the patient's nasal swab is collected and subsequently diluted in the provided buffer. To begin the test, the diluted sample is loaded into the sample port of the device using a fixed volume pipette, followed by pushing down three buttons in succession (1-2-3). The device is then plugged into a power source and a result is returned in < 30-minutes. Within the device, sample preparation (lysis, reverse transcription), amplification and detection are all automated with all required reagents stored on board. The sample preparation module houses a piston and on-chip valves in order to allow for the sample to enter the lysis module and rehydrate the stored RT enzyme and primers. Following lysis and reverse transcription, the mixture enters the mixing chamber and rehydrates the lyophilized PCR reagents. In order to carry out amplification, the device uses a "flow through" PCR method in which the sample-reagent mixture flows through two heat zones and carries out 40 amplification cycles via a serpentine channel.[44] Amplification creates biotinylated dsDNA, which flows to the detection module, and is immobilized onto the flow cell. The PCR products are detected using streptavidin coated with horseradish peroxidase, and a color changing substrate, leading to the formation of a purple spot for qualitative detection.[79]

Lucira Health's COVID-19 All-In-One Test Kit was the first molecular diagnostic test to obtain EUA for at-home use (with a prescription) (**Figure 2A**).[80] The test uses isothermal amplification, specifically RT-LAMP, to detect the N gene of SARS-CoV-2 in 11-30 minutes.[81] While the device does not incorporate traditional microfluidics, it simplifies test operation by preloading reagents, including lysis buffer, into a vial. Following sample collection, the user inserts and stirs the swab in the vial to elute and lyse the sample. The vial is then pressed down

to engage with the test unit, which allows the lysate to enter the fluidic module and fill the reaction chambers. An electronic heating component detects this filling and initiates isothermal amplification, which results in a change in pH and color change of the reaction mix. This color change is detected in real-time with on-board optics in a portable reader and output to the user with LED indicators. While the reader is battery powered and operates on its own, the test also interfaces with an app which allows users to record test results, and transmit them to health authorities.[82]

Cue Health's Cue COVID-19 Test was the first molecular diagnostic test to receive FDA EUA for home use without a prescription.[83] The device is composed of a portable and reusable reader, a single-use test cartridge, a disposable sample wand for specimen collection, and a mobile app for instructions and result readout. The test uses isothermal amplification to detect the N gene of SARS-CoV-2. Prior to initiating the test, the test cartridge must be inserted into the reader in order to initiate heating. The user collects a nasal specimen with a sample wand, and inserts the wand into the test cartridge to initiate sample preparation, which includes sonication to induce the mixing and binding of target analytes, with magnetic particles present among reagents in the reservoir. Isothermal amplification takes place in the sample reservoir using forward primers and reverse primers for the N gene conjugated to biotin and horseradish peroxidase (HRP) respectively. Heat-actuated valves allow for fluid to flow through via capillary action to the analysis reservoir where HRP is localized on an electrode. HRP then oxidizes a substrate that is applied, leading to a current measured by the electrode.[84] After 25 minutes, a semi quantitative nanoampere measurement is converted into a positive or negative reading. The test results are presented to the user on an app, stored on cloud servers, and reported to public health authorities.[77]

2.1.2 Antigen Tests

Overview

Antigen tests detect specific viral proteins that are present in patient specimens during active infections.[5] SARS-CoV-2 antigen tests specifically target the nucleocapsid or spike proteins in both nasal swabs and saliva samples.[85] Prior to the pandemic, POC antigen tests have been explored for detection of active infection in low- and middle-income countries (e.g., HIV, malaria, and tuberculosis), but it has been challenging to match the sensitivity of nucleic acid tests (**Supplementary Table 1 and 2**). For SARS-CoV-2, a number of tests have been deployed and have provided a useful alternative to molecular diagnostic tests to enable widespread testing in decentralized settings. The sensitivity of antigen tests varies depending on when the sample is taken during the time course of infection (according to the CDC). While studies have shown comparable sensitivity to nucleic acid tests at high viral loads, antigen tests are more likely to give false negative results especially when testing asymptomatic patients. To counteract decreased sensitivity, it is recommended to conduct serial testing over several days to catch these asymptomatic infections, and the FDA has issued EUAs to rapid antigen tests for such a use case[86]; indeed, recent studies have demonstrated real-world evidence that serial antigen testing every 3 days improves sensitivity.[87]

Assay Chemistry

A typical rapid antigen test uses a lateral flow format with a colorimetric visual readout from AuNPs (20-40 nm) or latex beads.[88,89] As demonstrated by the Weigl group, efforts to improve sensitivity can be segmented into three categories: reaction, transport, and signal

development.[90] In particular, the SARS-CoV-2 pandemic has accelerated advances in reaction and signal development.

Most commonly, monoclonal antibody pairs are used to capture and detect antigens,[91] but identifying or developing a successful pair can be time-consuming.[92] During the pandemic, after an initial period of development,[93] the first rapid antigen test (Quidel Sofia 2 SARS Antigen FIA) received EUA on May 9th, 2020.[94] Efforts to identify capture reagents continued, for example via an automated liquid-handling robot.[95] Using this method, over 1,000 anti-nucleocapsid antibody pairs were screened to identify pairs with the highest affinity for epitopes on the nucleocapsid protein,[96–98] and a similar process was carried out for the spike protein.[99]

As a potential alternative to antibodies, other capture reagents are being explored. For example, DNA-based aptamers targeting the spike protein are being developed,[100,101] based on previous work for detecting dengue.[102] Another effort includes using nanobodies, which can be expressed in bacteria,[103] for a rapid SARS-CoV-2 antigen test.[104]

To address low sensitivity of traditional antigen tests, novel signal development techniques were investigated.[105–107] For SARS-CoV-2 detection, quantum dots (Ellume) and luminescent nanoparticles (Luminostics) have been demonstrated to improve sensitivity.[108] (The use of low-cost optics to read fluorescence signals further improve sensitivity, as we discuss later in commercial case studies.) While we are not aware of independent testing of a reference panel comparing the performance of EUA antigen tests (as it has been done in a limited manner with antibody tests,[109] the Quidel QuickVue test (using a traditional colorimetric readout) has a self-reported LOD of 19,100 $TCID_{50}$/mL using heat inactivated virus. The Ellume test has an LOD of $10^{3.8}$ (~6,310) $TCID_{50}$/mL with heat inactivated virus, and the Luminostics test has an LOD of 880 $TCID_{50}$/mL with gamma irradiated virus (**Supplementary Table 2**). These results, albeit

reported by the manufacturers, demonstrate the potential for up to 20x improvement in sensitivity over standard rapid antigen tests.

Microfluidics

While LFAs automates assay operation, it can only do so for a limited number of steps. In its simplest form, an LFA automates wicking of sample, rehydration of reagents (including the reporter), and visual signal detection.[108] Most SARS-CoV-2 antigen tests follow this principle, differing in the antigen being detected and signal reporter of choice.

Use of plastic microfluidics opens the possibility of automating additional assay operations that can enhance performance and more closely mimic an enzyme-linked immunosorbent assay (ELISA), the gold-standard in immunoassays. Our lab has developed a platform in the past for HIV[110], syphilis[111], and Lyme disease.[112] In the pandemic, a number of efforts have pursued traditional microfluidic platforms for SARS-CoV-2 detection to allow for multiplexing,[113] and aid sample preparation.[114] Out of the current EUA approved tests for antigen detection, LumiraDx is the sole test that does not use a standard LFA. Instead, a microfluidic chip contains multiple independent assay channels that can be used for multiplexed testing, including running replicates or process control.[115] Applying a magnetic field to the microfluidic chip concentrates the SARS-CoV-2 immune complexes for signal generation, while unbound labels and sample are washed away from the measurement zone.[116] This format more closely mimics lab-based immunoassays than LFAs.

Following the success of using saliva matrix in nucleic acid tests, similar efforts were made to develop saliva-based rapid antigen tests in order to simplify sample collection;[117] however, they showed lackluster performance in initial studies,[118] such as low sensitivity.[119]

Connected Instrument

Unlike molecular testing, rapid antigen testing largely does not rely on instrumentation for assay operation as many of the steps are self-contained and automated with the LFA. Here, instrumentation focuses on improving sensitivity and lowering the LOD by quantifying the signal output from LFAs.

The first two antigen tests to receive EUA by the FDA were from BD and Quidel, which already had established platforms utilizing a dedicated LFA reader. BD uses a AuNP signal enhancement method for visual detection on a lateral flow strip and incorporates a handheld reader, BD Veritor Plus, to interpret results.[120] The Quidel test uses the Sofia 2 benchtop system that incorporates fluorescent detection with a UV LED source. It has a built-in touch screen interface to run the assay and report results.[121] However, these readers can still be a significant capital investment, providing a barrier for widespread adoption.[93] Nonetheless, Quidel has also received EUA for another rapid antigen test, the QuickVue SARS Antigen Test; their EUA allows for POC testing in facilities operating under a CLIA waiver, and more recently, for prescription home use as well as over-the-counter (OTC) home use.[122,123] Test results are meant to be interpreted by the naked eye, removing the need for an external instrument. Another visual rapid antigen test is the Abbot BinaxNOW. The Abbott BinaxNOW COVID-19 Ag Card has EUA for use in CLIA certified laboratories as well as EUA for prescription home use when supervised by a telehealth proctor.[124] To provide this service, Abbott has partnered with eMed, a telemedicine platform,[125] which also allows users to store, access, and display COVID-19 test results. More recently, the test has received EUA for a self-test (without supervision) and is available without a prescription.[126] In summary, this use of a connected instrument allows users

to access the POC antigen test in three ways: OTC self-test, proctored at-home test, or at a healthcare facility.

With developments in low-cost and miniature optics, efforts are also being made to create cheap, low-profile readers for lateral flow tests.[127,128] For example, Lumos has helped numerous companies develop custom POC readers, and offers an off the shelf product, the Leelu reader.[129] Another company, Jana Care, has developed the Aina device, a colorimetric and fluorescent reader for paper diagnostics that is compact and affordable,[130,131] and runs the Aina Open program to put the device in the hands of test developers. For SARS-CoV-2 detection, Ellume developed disposable test cartridges with integrated optics for fluorescent detection;[132,133] here, a smartphone controls the operation, processes the signal, and displays the result, hence reducing the technical requirements and cost of the reader.

There also has been interest in replacing the reader all together with a smartphone, by using the camera lens for imaging and processing power of the phone for interpretation of test results.[134] This has also opened the door for other test enhancements such as providing step-by-step instructions, as well as automated result analysis and reporting to parties of interest. To this end, various partnerships are taking place. For example, BD is working with Scanwell Health to adapt their rapid test for at-home use.[135] Our lab has previously demonstrated the utility of a smartphone application that in addition to guiding the user, can also use machine learning to automate the rapid interpretation of the INSTI Multiplex HIV-1/HIV-2/Syphilis Antibody Test.[136,137] We have also recently developed a deep-learning approach that would facilitate rapid adaptation of the model to different line-based rapid test kits, and partnered with a company (Safe Health System) to incorporate this algorithm into a smartphone app that can interpret rapid

antigen tests within a telemedicine platform. We will further discuss these developments in **Section 2.2: Data Analytics**.

Commercial Case Studies

Here we discuss three commercial POC SARS-CoV-2 antigen tests that highlight novel assay chemistry, microfluidics, or instrumentation (a larger overview of antigen tests is provided in **Table 1** and **Table 3)**. Performance data collected from company EUA documentation is summarized in **Supplementary Table 2**. Emphasizing the push towards POC use and also home use, we discuss user steps and the design of technological elements that enable a streamlined workflow.

Ellume's COVID-19 Home Test (Figure 2D) was the first OTC, home-use test granted EUA by the FDA.[138] The test uses a standard lateral flow format, but incorporates quantum dot fluorescent nanoparticles along with a disposable, battery-powered, smartphone connected reader (Analyzer).[139] A mobile application relays step-by-step instruction to a user, and allows a user to view results. The results can then be shared with healthcare providers and is reported in real time to public health authorities for disease mapping. The first step in running the test is adding the processing fluid containing a fluorophore to the dropper. After collecting a patient sample, the nasal swab is clicked-in with the dropper to release the viral antigens into the processing fluid, where fluorophores bind to viral nucleocapsid protein in the sample. A few drops of this liquid containing the fluorophore-labelled antigen complexes are added to the sample port of the Analyzer, where it is wicked into the test strip via capillary action in the LFA. The LFA contains immobilized antibodies specific to SARS-CoV-2 nucleocapsid to capture the fluorophore labelled antigen complex on the membrane. Fluorescence intensity is detected via a disposable, inexpensive optoelectronic reader within the Analyzer. The fluorescence intensity is read, then

interpreted with a microprocessor that sends the results to the connected smartphone. After the sample is added, the entire procedure takes 15 minutes to generate a result.

Luminostics Clip COVID Rapid Antigen Test (**Figure 2E**) uses a LFA format along with strontium aluminate persistent luminescent nanoparticles (PLNPs) that provide a long-lasting glow following excitation, and can be both excited and imaged with a smartphone camera.[140–143] This test first involves inserting a cartridge (containing the LFA strip and sample well) into the Clip Analyzer, which consists of an Apple iPhone, a battered-powered adaptor around the phone, and the 'Clip COVID' mobile application to run the test and provide a user interface. To run the test, an anterior nasal sample is collected and mixed with buffer in the provided "Extraction Tube." This tube is then capped with the provided dropper tip and all of the antigen-buffer mix is dispensed onto the sample well of the cartridge. This sample flows through the LFA test strip via capillary action, where SARS-CoV-2 nucleocapsid protein is captured and labeled with PLNPs. The iPhone camera flash is used to briefly excite the nanoparticles and the camera lens captures images of the nanoparticle luminescence associated with the presence of the antigen. Here, usage of the time-gating imaging technique eliminates the need for expensive optical filters and light sources on the Analyzer, reducing the cost of the device. The captured image is analyzed by the mobile application using artificial intelligence and test results are displayed on the application screen within thirty minutes.[144]

LumiraDx's SARS-CoV-2 Ag Test (Figure 2F) uses a microfluidic "test-strip" to conduct an immunofluorescence assay with a portable, connected instrument. The instrument contains an RFID strip code reader to calibrate lots, electronics to control fluid movement, optics for fluorescence measurement, and a touch screen to run the test and view results.[145] The instrument can be run in three different modes depending on the connectivity requirements: 1)

standalone, 2) managed (one or more devices connected to Connect Manager application via hub or smartphone), or 3) EHR connected (for transfer of patient results).[146] To run the test, an anterior nasal or NP swab sample is collected and eluted in an extraction buffer. A single drop of this sample-buffer mix is added to the test strip via the provided vial dropper. SARS-CoV-2 specific antibodies are used to capture the nucleocapsid protein and a magnetic field is applied, which causes magnetic particles associated with the formed antigen-antibody immune complexes to be retained, and the rest of the unbound sample to be removed from the measurement zone. This allows the instrument to measure the immune complexes labeled with fluorescent latex particles in a dry state,[147] with their fluorescence proportional to the concentration of antigen particles in the sample.[115] Test results are displayed on the instrument screen within twelve minutes.

2.1.3 Antibody Tests

Overview

Antibody tests, or serology tests, detect antibodies produced by the body's adaptive immune response, and indicate a prior infection. As is the case for many infectious diseases, infection with SARS-CoV-2 leads to sustained antibody levels.[148–150] Typically, antibodies are measured by conducting an immunoassay on blood. The gold-standard laboratory method is the enzyme-linked immunosorbent assay (ELISA). Indeed, laboratory-based ELISA for detecting antibodies against SARS-CoV-2 immunogens are highly accurate.[151,152]

For SARS-CoV-2, detection of antibodies is a valuable public health tool as it can identify prior infected asymptomatic cases and therefore better quantify total case numbers.[153] Nevertheless, although detection of antibodies is a routine method for assessing health status and immunity status for many infectious diseases, it has not yet been widely deployed during the

COVID-19 pandemic. Early in the pandemic, due to the urgency of the crisis and strong precedence and acceptance of antibody tests for many infectious diseases, the FDA loosened regulations for developers to offer SARS-CoV-2 rapid antibody tests to healthcare workers with only self-reported results.[154] Many LFA tests were offered in the market, some of dubious quality, before the regulation was changed.[154,155]

Assay Chemistry

Rapid antibody tests use one of three immune sandwich strategies to create a colorimetric signal on the paper substrate.[156] As many tests differentiate between IgG and IgM response, anti-human IgG and IgM antibodies are used as capture reagents, and SARS-CoV-2 proteins (spike or nucleocapsid) are conjugated to a reporter (e.g., gold or latex nanoparticles) visible to the naked eye. The second strategy uses SARS-CoV-2 antigens as a capture, and conjugated anti-human antibodies as the reporter. This strategy allows for detection of total antibodies against SARS-CoV-2, unless different color markers are used for different antibody isotypes. A third strategy of a double antigen immunosandwich has also used for detection of total antibodies (see section on **NOWDiagnostics's ADEXUSDx COVID-19 Test**).

The initial accelerated development of antibody lateral flow tests[157] was made possible via utilization of off-the-shelf components as well as relaxed regulatory guidance (**Section 2.4 and Figure 5A**). Polyclonal human antibodies can be purchased with and without conjugation to common reporters like AuNPs from a variety of vendors. The major additional step in the development process is the purification of SARS-CoV-2 proteins (nucleocapsid, and spike) which was done at groundbreaking speeds by companies and laboratories across the country. In fact, by the end of March 2020, 37 companies had already informed the FDA of an introduction of a serology test onto the market.[154]

An important goal of antibody tests was to guide decisions on reopening society safely by determining immunity to SARS-CoV-2. However, at the onset of the pandemic, rapid antibody tests suffered from poor performance.[157] Adding to the confusion, it was not yet established, as it is now, that prior infection leads to sustained antibody levels,[148–150] and that prior infection leads to immunity.[158] Now that we now know the detection of antibodies indicates prior infection and hence immunity, detection of neutralizing antibodies (Nabs) can further shed light on the level of protective immunity achieved in subjects.[159] Nabs target the SARS-CoV-2 spike trimer and have the ability to block the virus from binding to the human angiotensin converting enzyme (hACE2) receptor, thereby inhibiting infection.[160,161] Traditionally, Nabs are detected with virus neutralization assays, using live virus or pseudovirus. However, these involve complex, time-consuming procedures that can require BSL-3 clearance if using live virus.[162,163] A simpler assay that mimics the interaction between the virus and human cells using purified receptor binding domain (RBD) protein and ACE2 was developed. In November 2020, the test, called the cPass SARS-CoV-2 Neutralization Antibody Detection Kit, received EUA as the first test to detect Nabs for SARS-Cov-2.[164] In this assay, the test signal is inversely proportional to the concentration of Nabs, as any Nabs present in the sample will prevent labeled RBD proteins from binding to immobilized ACE2 in the assay. There have also been efforts to transport this assay to a POC format by using a lateral flow format and AuNPs for a colorimetric readout. This includes tests developed by multiple companies,[165–168] which are marketed as inexpensive and rapid methods to track the effectiveness of vaccines. However, it is important to note that immunity can still be achieved through memory B- and T-cells without high levels of neutralizing antibodies.[169,170]

As in rapid antigen tests, developers of rapid antibody tests experimented with novel reporter molecules to improve sensitivity. While a majority of the commercial rapid antibody tests use standard reporter molecules (e.g., AuNPs), researchers have demonstrated other novel reporters in literature such as selenium nanoparticles,[171] or gold nanoshells.[172]

Microfluidics

The format for fluidics and assay integration for rapid antibody tests is similar to that of rapid antigen tests, with most based on LFAs. Before the pandemic, LFAs had been extensively used around the world for antibody testing, including for HIV and malaria. While there have been developments of plastic microfluidic devices that can allow for multiplexing,[113,173] the LFA has remained the dominant commercial platform. Additional fluidic innovations for paper-based assays were investigated, including an electrochemical platform,[174] paper-based ELISA[175,176], and a vertical flow format.[177]

Given the fact that antigen and antibody tests are typically identified with an immunoassay, microfluidic platforms designed for either can easily be adjusted for antigen or antibody detection by the selection of new capture and detection reagents. Multiple companies have demonstrated this ability by developing both rapid antibody and rapid antigen tests (e.g., LumiraDx, LightDeck). For antibody detection, the differentiating factor is the sample type needed as rapid antigen tests require respiratory samples and rapid antibody tests largely require whole blood or serum samples.[178] To use whole blood, a plasma separation membrane is incorporated to trap red blood cells that would otherwise interfere with visual detection.[179]

For POC use, rapid antibody tests typically use a fingerstick whole blood sample[180] with SARS-CoV-2 tests typically requiring a 10 μL sample.[181] The fingerstick method offers a quick, less painful alternative to a venous blood draw which needs to be done by a trained technician.

While the method opens the door for at-home collection and testing of blood samples,[182] the procedure itself can be prone to errors, produce variable sample volume and sample contents.[183–185] In fact, studies on at-home HIV testing have shown users have difficulty with blood sampling.[186] Usability studies conducted in the United Kingdom for at-home testing of SARS-CoV-2 antibodies also demonstrated users having difficulty with sample collection.[187,188]

Prior to the pandemic, researchers have been developing alternative capillary blood collection methods. For example, Seventh Sense Biosystems (now rebranded as "Your Bio") created the TAP device that uses an array of microneedles and a vacuum to collect blood from the upper arm area.[189] While the current design collected blood to be sent to a laboratory, the company has had discussions with test developers on combining their method with POC devices.[183] Another company Tasso, which recently received EUA as an at-home blood collection device for SARS-CoV-2 antibody testing, also uses microneedle technology.[190] While there are numerous research articles on alternative blood collection methods for rapid tests,[191–193] almost all rapid antibody tests currently approved for SARS-CoV-2 use a basic lancet and capillary for blood collection. An exception is a platform from NOWdiagnostics that incorporates a capillary into the test device, only requiring a separate lancet for blood collection. Additionally, the test does not require additional application of buffer, thereby minimizing the number of external components required for blood collection and potentially simplifying the sample collection process. Nonetheless, the area of blood microsampling for at-home testing is a field ready for innovation.

Moreover, as an alternative to invasive blood sampling, recent studies have also demonstrated the ability to detect antibodies against SARS-CoV-2 in saliva samples.[194–196]. Saliva sampling provides a non-invasive collection method as opposed to blood collection, simplifying

the process.[5] While there are no current COVID-19 antibody tests using saliva samples that have received EUA, it is being investigated[197,198] as a method to greatly expand serosurveillance.

Connected Instrument

When the first rapid antibody tests were released for SARS-CoV-2, many were traditional visual read LFAs that required user interpretation. An example of such a test includes the Assure COVID-19 IgG/IgM Rapid Test from Assure Tech which detects both anti-nucleocapsid and anti-spike antibodies, and uses a visual readout with AuNPs.[199] Another example is the ACON SARS-CoV-2 IgG/IgM Rapid Test, which also uses a visual readout with AuNPs, creating a red band. However, visually interpreting LFAs can be subjective, especially at low analyte levels where bands can be difficult to distinguish.[188] This problem is compounded with use in decentralized settings, where users are likely untrained in device operation. Therefore, there have been efforts to automate interpretation of these LFAs using image processing algorithms on smartphones. Adding to our previous discussion on this topic for rapid antigen testing, we discuss two more examples here for rapid antibody testing. Abingdon Health has developed a reader, which they offer as a contract service to be adapted to any LFA.[200] The app uses image processing technology to generate data on visual test lines, provides a user interface on the phone, and a data management hub. Another company, BBI solutions, markets their Novarum technology which also turns any smartphone into a mobile diagnostic platform. The app provides functionality for pre, during and post scan workflow, with the functionalities described in more detail here.[201]

Commercial Case Studies

Here we discuss three commercial POC SARS-CoV-2 antibody tests that highlight novel assay chemistry, microfluidics, or instrumentation (a larger overview of antibody tests is

provided in **Table 1** and **Table 4)**. Emphasizing the push towards POC use and also home use, we discuss user steps and the design of technological elements that enable a streamlined workflow.

AssureTech's Assure COVID-19 IgG/IgM Rapid Test Device (Figure 2G) was the first antibody test for COVID-19 to receive an EUA for POC use, on September 23, 2020.[199] It is a lateral flow immunoassay that detects antibodies against the nucleocapsid and spike (S1) proteins in fingerstick whole blood. Immobilized on the test strip's nitrocellulose membrane is anti-human IgM (IgM Test Line), anti-human IgG (IgG Test Line), and goat anti-mouse IgG (Control Line). The conjugate pad contains recombinant SARS-CoV-2 antigen (nucleocapsid and spike (S1 protein) conjugated with AuNPs. Once the whole blood sample is added to the sample port, along with running buffer, SARS-CoV-2 specific antibodies in the sample bind with the gold conjugates and if anti-SARS-CoV-2 IgM and/or IgG antibodies are present, they will form immune complexes at the respective test lines, generating a red, visual band. If the membrane properly wicks, the control line will change from blue to red. A test result is generated in 15 minutes, after which an operator visually interprets the test bands.[199]

NOWDiagnostics's ADEXUSDx COVID-19 Test (Figure 2H) is a double antigen sandwich lateral flow immunoassay that detects total antibodies against SARS-CoV-2 in fingerstick whole blood samples.[202] Of note, the test does not require additional reagents, equipment, or buffers, unlike previously described LFA tests.[203] The test uses microfluidics to wick blood through the sample application zone and onto the LFA.[204] Here, the sample is first wicked through a plasma separation membrane, to remove red blood cells. The membrane also contains dried colloidal gold conjugated to recombinant SARS-CoV-2 S1 receptor binding domain (RBD) antigen as well as colloidal gold conjugated to rabbit IgG. Antibodies against

SARS-CoV-2 in the sample bind to gold labeled RBD antigen, which is captured downstream by immobilized S1 RBD antigen at the test line. A red, visual line indicates a detectable level of anti-SARS-CoV-2 antibodies. The gold labeled Rabbit IgG will bind to polyclonal anti-rabbit IgG forming a visual control line if proper wicking is achieved. Results can be seen in about 15 minutes, after which a user visually interprets the bands. While not included in the FDA EUA, the company has also developed the ADEXUSDx analyzer, a portable handheld instrument to automate result interpretation, and is developing the DxREADER, which is a more portable reader that connects to a smartphone.[205]

JoysBio's SARS-CoV-2 IgG/Neutralizing Antibody Rapid Test Kit (Figure 2I) is a CE-marked lateral flow test kit that detects both IgG and Nabs against SARS-CoV-2 in fingerstick whole blood samples.[167] The test kit contains SARS-CoV-2 recombinant antigen (RBD and nucleocapsid), and Chicken IgY labeled with colloidal gold. The nitrocellulose membrane is immobilized with mouse anti-human IgG (test line 1), hACE2 (test line 2), and goat anti-chicken IgY (control line). To detect Nabs, the assay mimics the virus neutralization process; when a sample is added to the test, Nabs in the sample bind to RBD labeled with colloidal gold and block the interaction between RBD and hACE2 at test line 2. Non-neutralizing antibodies against SARS-CoV-2 also bind to RBD labeled with gold, and this complex along with unbound gold is also captured at test line 2. The intensity of the test line is inversely proportional to the level of RBD specific Nabs antibodies (i.e., a faint line indicate high levels of Nabs). Next, gold labeled, non-neutralizing antibodies against SARS-CoV-2 are captured at test line 1 by mouse anti-human IgG. Finally, chicken IgG labeled with colloidal gold binds to anti-chicken IgY immobilized at the control line. Between 25-30 min after sample addition, the

results are read with the first band corresponding to Nabs, the second to IgG antibody, and the third for the control line.

2.1.4 Emerging Technologies

Face Mask

The SARS-CoV-2 pandemic has spurred a rethinking of how to rapidly diagnose infectious diseases.[3] A unique development has been widespread use of face coverings to reduce transmission of the virus, which has prompted researchers to pursue virus detection masks. For example, SARS-CoV-2 protease-detecting test strips can be attached to N95, surgical or cloth masks.[206] If the user is infected, proteases specific to SARS-CoV-2 (Mpro and PLP, which are required for virus replication) are exhaled in the breath and accumulate in the test strip. After the period of wear, the user squeezes a blister pack containing nanoparticles that change color in the presence of the SARS-CoV-2 proteases, allowing visual indication of infection and a positive control. The test strips can be mass produced via roll-to-roll processing, allowing low cost for daily use. Another mask-attachable visual test integrates a freeze-dried diagnostic COVID-19 test that is activated by a blister back of water, based on a platform to detect RNA in exhaled breath.[207]

Breathalyzer

Breathalyzers that can detect volatile molecules from a patient's exhaled breath had been in development before the pandemic. For SARS-CoV-2, a device has been tested in Netherlands that analyzes volatile chemical composition of exhaled breath using seven metal oxide semiconductor sensors, and used for screening purposes by the Dutch government before use was halted due to insufficient sensitivity.[208] Another device, from developers in China, uses a

nanomaterial-based sensor array with multiplexed capabilities to detect and monitor COVID-19. When conjugated AuNPs in the device bind to volatile organic compounds in exhaled breath, the nanoparticle film swells or shrinks, causing changes in the electric resistance which can be interpreted for disease detection.[209] The reported sensitivity and specificity for current breathalyzer tests are over 90%, but the devices generally need to be validated independently and on larger sample sizes before commercial use.

T-cell Test

Following infection or vaccination, in addition to the humoral response generated by B cells, there is a cell-mediated response primarily carried out by T cells.[210] Before SARS-CoV-2, an application of T cell counting was the measurement of total CD4+ T cells in HIV patients to identify virally-suppressed immune systems, and have even been developed by commercial entities (e.g. BD FACSPresto or Abbott PIMA) for low-resource areas.[211–214] However, it is technologically more challenging to measure virus-specific T cells. Traditional procedures to do so (i.e., ELISpot or intracellular cytokine staining) are time consuming and lack sensitivity.[215] With renewed interest in understanding the role of T cell immunity in fighting SARS-CoV-2 and how they provide resistance to reinfection, several companies have developed alternative protocols. This includes a test from Adaptive Biotechnologies which recently received FDA EUA, becoming the first test to detect T cells.[216] Towards POC use, a skin test for SARS-CoV-2 T cells, akin to a TB skin test, is in development; the assay uses synthetic peptides to generate an immune response at the dermal layer, with the measurement of the raised region on the skin roughly equating to the amount of T cell immunity.[217,218] A rapid T cell test using a cytokine release assay is also being developed.[219–221] Overall, POC T cell tests[222] could complement

antibody testing for identifying past infections via identification of cell-mediated immunity (especially with waning levels of humoral immunity).[222]

2.2 Data Analytics

The Coronavirus Aid, Relief, and Economic Security (CARES) act requires "every laboratory that performs or analyzes a test that is intended to detect SARS-CoV-2 or to diagnose a possible case of COVID-19" to report the results from each such test to the Secretary of the Department of Health and Human Services (HHS)."[223] This guideline includes all facilities performing POC tests or tests utilizing at-home specimen collection. HHS also outlines the methods for submission (including to state or local public health departments) and required data elements in the guidance document.[223]

However, the increase use of POC testing conducted outside of traditional healthcare settings, presents challenges to this reporting model. According to HHS, "more FDA-authorized rapid diagnostics, such as point-of-care, over-the-counter, and at-home tests, are increasingly being used but often lack an easy way for users, such as schools, nursing homes, or businesses, to report results." For example, in an initial pilot study of a rapid antigen test in schools, reporting needs required significant staff time and expertise.[224]

The HHS guideline document[223] suggests decentralized test results can be reported via applications on smartphones or tablets, a patient portal, or direct transmission from the test itself. Some test developers have taken this on. While custom smartphone apps are being built to connect rapid test results to health authorities,[225] HSS has launched a "COVID-19 At-Anywhere Diagnostic Design-a-thon" to encourage development of additional digital tools to enable automated data capture, transmission, and analysis.[226]

Solutions included a platform from Oracle, which allows submission of test results directly from mobile apps, test manufacturers, or administrator networks and improves the confidentiality, integrity, and immutability of test reporting using a blockchain platform.[227] Another solution includes a blockchain network to collect data from patients using OTC tests, and scan devices for authentication,[228] and information-capture methods (i.e., smartphone apps, web-based apps, automated phone line attendants, and self-service kiosks) with real-time data analysis.[229]

A further design sprint ("COVID-19 TOPx Tech Sprint") poses the problem statement as "1) help state and local public health authorities track and understand the virus in populations and communities, 2) help stakeholders outside of healthcare make key operational decision and 3) help consumers and business manage point-of-care testing data outside lab settings."[230] Hence, in addition to reporting results, there is also a need to aggregate and analyze data from testing done outside of laboratories. While custom solutions are being developed to provide organizations the ability to manage their testing programs by viewing aggregated results,[231] digital solutions that span testing platforms may be most effective. Another possible solution is to provide connectivity to third-party platforms that aggregate other medical records. For example, the company CLEAR, which developed a mobile technology to link personal information to biometric data, has created a Health Pass to store medical information that includes test results and vaccine status,[232,233] and has partnered with the National Basketball Association[234,235] to enable health screening and connect to a software platform from a POC rapid test.[236] This third-party integration allows fans who conduct testing at home to verify their test result and enter the arena.

At-home POC testing will pose another challenge for how patient data and test results can be collected and reported, given their importance to public health efforts.[223] Therefore, developers of new POC tests will need to consider various solutions for data reporting, and if they would like to develop an in-house solution, or partner with another company. Additionally, considerations will be need to be made regarding connectivity to other mobile technologies that look to aggregate various other medical information. This has implications for downstream regulatory approval as it of interest to the FDA for authorizing OTC tests. For example, in granting Lucira Health authorization for OTC use, the FDA stipulated that the company must develop "a mobile phone application or website to further facilitate results reporting by both the healthcare provider and the individual using your product",[237] prompting them to release LUCI pass. Future OTC approvals may require solutions for data reporting and integration.

2.3 Clinical Workflow

For years before the pandemic, POC diagnostics had begun to be widely implemented in decentralized healthcare settings, with increased use and approval by healthcare professionals,[2] and also by consumers at a slow but steadily growing pace. For example, an increase in OTC tests approved by the FDA (**Figure 3**) reflect an increased acceptance and interest in such tests by both consumers and the FDA. However, most OTC tests focus on testing for drugs or chronic conditions like diabetes or cardiovascular health, with the only infectious disease test approved for home use and available OTC being the Oraquick HIV test kit.[238]

The COVID-19 pandemic resulted in an acceleration in the authorization of tests for POC and OTC use. In the early stages of the pandemic, many areas in the US experienced a shortage of testing options and resources, including reagents and testing infrastructure,[1] leading to increased transmission rates, hospitalizations, and deaths. POC diagnostics presented a viable

solution to fulfill the need for increased testing by increasing accessibility, including in pharmacies, urgent care clinics, hospitals, and mobile testing sites set up by the federal, state, or local governments (we will discuss use cases in **Section 3** in greater depth).

Towards at-home testing, the first set of tests were sample collection kits that could be mailed to homes but required mailing the samples back to a lab. LabCorp offered the first at-home collection kit that garnered FDA EUA, to self-collect a nasal swab without a prescription.[239] On December 15, 2020, the FDA granted EUA for Ellume's home test, the first OTC, fully at-home test for COVID-19.[138] This movement of accessible, and at-home testing continues to headway as self-administered tests, such as Ellume's and Abbott's antigen tests, become readily available in pharmacies.[240] Now, molecular diagnostics tests are available for OTC use (Lucira and Cue Health) with Lucira's test available for purchase online.[241] With a number of OTC testing options available, consumers are able to obtain reasonably accurate COVID-19 tests from the privacy, convenience, and safety of their own homes.

2.4 Regulatory Guidance

On February 4th, 2020, the Secretary of HHS declared a public health emergency due to SARS-CoV-2, which under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), allows the FDA to "emergency use authorize" unapproved drugs, devices, or biological products.[242] The minimum requirement for EUA is that the known and potential benefits outweigh the potential risk, even if there is not yet enough evidence to fully establish its safety and effectiveness. EUA is a relatively new concept for the FDA, with the first EUA granted in 2009 during the H1N1 pandemic. In addition to SARS-CoV-2, there are current EUAs in place for Ebola, Enterovirus D68 (EV-D68), H7N9 Influenza, Middle East Respiratory Syndrome

Coronavirus (MERS-CoV), and Zika virus (**Figure 4A**, which further summarizes the number of IVDs that have received EUA for each public health emergency by assay type).

EUA enabled SARS-CoV-2 diagnostic tests to be developed, validated, and deployed in weeks rather than the many months or years it traditionally takes.[243] To facilitate submission, the FDA put together templates for various types of SARS-CoV-2 tests (e.g., molecular diagnostics, antigen test. antibody tests).[243] Developers can also submit a pre-EUA to begin discussions with the FDA and gain guidance on their submissions. Example metrics include LOD, inclusivity, cross-reactivity, and clinical evaluation.[244] Such changes to the regulatory environment played a role (among others) in the vast increase in number of IVDs EUA compared to past public health emergencies (**Figure 4A**). Further, **Figure 4B** stratifies the SARS-CoV-2 tests that obtained EUA by its authorized setting of laboratory, POC, or OTC use.

Early in the pandemic, the FDA recognized the need for rapid antibody testing as a means to better understand COVID-19 from a scientific perspective and inform the government response.[154] On March 16, 2020, the FDA published guidance to facilitate access to these tests and began allowing developers to market serological tests without EUA as long as the test was validated, the FDA was notified, and test reports included limitations. Soon, the market was flooded with serology tests, and by the end of April 2020, the FDA had received 164 notifications for serological test use without EUA, many of which were eventually shown to perform poorly. As of Feb 1st, 2021 the FDA had removed 225 listings, issued 15 warning letters, and placed 88 firms on import alert for violations of misused serological test kits and false claims.[154] During this time, the FDA began working with the NIH, CDC, the Biomedical Advanced Research and Development Authority (BARDA), and the National Cancer Institute

(NCI) to order to establish the capacity to evaluate serology tests independently, the first time the federal government has performed evaluations of FDA authorized tests itself.[154]

Of potential interest to POC test developers, the Director of the Center for Devices and Radiological Health (CDRH) at the FDA outlined the lessons learned from the EUA process for SARS-CoV-2 diagnostics, for molecular[243] and serology testing.[154] Following the experiment with antibody testing, he stated that the FDA would not repeat the guidance allowing for antibody tests to enter the market before review. The perspectives also suggest it would be more effective in the next public health emergency, to focus development and validation efforts on a few tests, instead of scores of tests (**Figure 4**) in order to efficiently use resources. Finally, what would have implications even outside of a public health emergency, the FDA recognized the need for a federal government agency or group on its behalf have the capacity to independently evaluate tests. By streamlining the validation of tests, this will provide a common frame of reference to compare test performance, minimize the need for developers to find clinical specimens, and overall expedite the approval process.

The loosening or strengthening of regulatory requirements by the FDA has been a continuing act to balance risks and benefits in authorizing the use of POC tests. Authorization of diagnostic tests without exemplary evidence of effectiveness carries risk in potential false positive and false negative diagnoses. This is especially harmful in the case of false negatives (low sensitivity), which may lead to potentially contagious individuals not self-quarantining due to false assurance from a negative test result. However, in a public health emergency, the potential benefits of alleviating overcrowded hospitals, reducing hospitalization and transmission rates, and ultimately saving lives through more accessible diagnostic tests may be worth the potential risk.

2.5 Reimbursement

A challenge in the deployment of POC tests has been the payor for the tests – whether it is the insurer or consumer, and eligibility requirements for insurance coverage. For the pandemic, these questions were addressed in a swift manner to enable rapid deployment. On March 18, 2020, the Families First Coronavirus Response Act (FFCRA) was passed by Congress, mandating insurers to provide diagnostic test coverage for detecting SARS-CoV-2 without imposing any cost-sharing requirements. The mandate included deductibles, copayments, coinsurance, prior authorization, or other medical management requirements.[245] Testing coverage also applied to those who do not exhibit symptoms or suspect exposure to coronavirus.[246] Soon afterwards, the CARES Act enacted on March 27, 2020 further expanded the range of diagnostic items and services that were covered. Additionally, due to the Health Resources & Services Administration (HRSA) COVID-19 Uninsured Program, healthcare providers can submit claims for reimbursement to HRSA when providing COVID-19-related services to uninsured patients[247] (which include specimen collection, antigen and antibody testing, which can be done in an office, urgent care, emergency room, or telehealth setting[248]), but the patient is expected to cover the cost if the healthcare provider does not submit a claim to HRSA.[249] For instance, companies providing at-home COVID-19 collection kits (e.g., LetsGetChecked) will send a receipt to the patient who will in turn seek reimbursement from their insurer.

The situation is different for OTC use. For example, for rapid antigen tests, individuals can try to bill OTC test costs to insurers,[246] but many insurers may have restrictions such as requiring testing to be conducted by a healthcare professional.[250] At the moment, many OTC tests for SARS-CoV-2 must be covered out of pocket or through a health Flexible Spending Account

(FSA) or Health Reimbursement Account (HRA) which can be used to purchase any OTC test.[251] The rise of OTC testing certainly brings up questions regarding reimbursement and whether insurers will be required to cover them going forward. Either tests will need to be priced low enough (and designed accordingly) so reimbursement is not needed, or they will need to convince insurers of their benefit with studies demonstrating their benefit for health outcomes.[252] Nevertheless, current policy demonstrates consumers are willing to pay out of pocket for new POC tests if they perceive sufficient value.

2.6 Legislation

The severity of the pandemic called for immediate and massive investment by the government in technologies to help mitigate spread. One non-profit has tracked $5.93 trillion allocated to legislative efforts supporting responses to COVID-19.[253] Of this amount, $53.9 billion has been for "testing, monitoring, and R&D" and $46.6 billion to "preparedness and response."[253] Some of this funding supported R&D efforts, which included the Rapid Acceleration of Diagnostics (RADx) initiative and funding by BARDA. The RADx initiative was launched by the NIH with an initial investment of $1.5 billion, and in partnership with the Office of the Assistant Secretary of Health, Department of Defense (DoD), BARDA, and the FDA on April 29th, 2020.[254] The program sought technologies to enable accurate, fast, easy-to-use, and widely accessible testing, and is broken down into 4 programs. RADx Tech to focus on innovative POC and home-based tests, RADx-UP to focus on disparities and how to address them in underserved population, RADx Rad to support radical, non-traditional approaches, and RADx-ATP to increase capacity and throughput of more mature technologies. To date, 29 projects have progressed through multiple review stages in the RADx-Tech and RADx-ATP programs and it is estimated that the funding has contributed to increased capacity of 150 million

tests while reducing the normal multiyear commercialization process to about six months.[255] Additionally, BARDA itself has committed almost $14.5 billion to COVID-19 response, which includes diagnostics, therapeutics, and vaccines. While diagnostic funding only makes up about 1% of this number, this has brought in over $157 million dollars to aid in the development of numerous COVID-19 tests.[256] In fact, the agency notes its support of 22 EUAs for SARS-CoV-2 diagnostic tests and aided in shipping over 121 million test kits as of May, 28th, 2021.[257]

To visualize the impact of this funding on market entry of POC technologies, segmented by the maturity of the technology prior to the pandemic, we tabulated all the POC diagnostic devices that have received U.S. federal support (along with some additional tests) (**Figure 5**). Looking at devices that received EUA, interestingly, no company that has received an EUA was founded after 2015 (**Figure 5A**); in fact, a larger trend was that the companies that initially garnered EUA approval were longer established companies, with more recently founded companies taking more time to obtain EUA (**Figure 5A**). In terms of funds disbursed to companies in general, most government investments targeted companies founded from 2010-2015 (**Figure 5B**), although Quidel and Abbott, two established players in the IVD industry, received large sums of money to increase their production capacities and supply more tests.[258,259] The power of these investments in more recent technologies is further illustrated in that outside the established IVD players (outlined with a dashed box in **Figure 5C**), large government funding was correlated to short time to EUA. Thus, government funding potentially accelerated the commercialization of SARS-CoV-2 POC diagnostic devices, and allowed more recently developed technologies to receive EUA and be deployed to benefit the public.

2.7 Systems Integration

In the POC ecosystem (**Figure 1**) during the pandemic, how we consider the problem of "systems integration" has evolved. Previously, on the technology side, there has been an increasing realization that a successful POC diagnostic test must successfully integrate chemistry, fluidics, hardware, and software to ensure a "sample-to-result" workflow and seamless user experience.[2,52,260,261] The pandemic has required developers to also think about how their POC test integrates with public health reporting efforts and integration with data analysis technologies. On the non-technology side, the different issues on clinical workflow, reimbursement, regulatory guidance, and legislation are important in determining a path to market and adoption by users, and are synergistic with the technological components. However, the nuances of each component are informed by specific use cases, as different POC use cases have vastly different constraints and requirements. In the next section, we will discuss how the POC ecosystem has developed for four POC use cases for SARS-CoV-2 diagnostics.

3. Use Cases for SARS-CoV-2 POC Diagnostics

For a POC device, it is clear that general advantages in speed, low cost, and simplicity while maintaining gold-standard performance are desirable,[2,3] but different POC settings pose specific design constraints that must be considered during device development. In a previous review, we had outlined four different use cases for POC diagnostics, visualized in a 2x2 matrix based on available operating budget (low and moderate) and infrastructure (clinic and field setting).[2] In this section, we apply this framework to use cases for SARS-CoV-2 testing at the POC (**Figure 6**). For each use case, a descriptive name is provided (**Figure 6A**), as well as an analogy with consumer electronics to aid the visualization (**Figure 6B**). First, the **Premium Clinic** use case (with the electronics analogy "Laptop"), is the least resource constrained, as it

includes POC diagnostics used in clinical environments with relatively unrestricted costs (e.g., hospital emergency rooms, operating rooms, or intensive care units). Second, the **Economy Clinic** use case (with the electronics analogy "Tablet") is also conducted in a clinical setting but constrained by cost considerations relative to the Premium Clinic use case (e.g., urgent care clinics, physician offices, primary care clinics). Third, the **Premium Field** use case (with the electronics analogy "Smartphone") is constrained by portability considerations (in the field), but not cost (e.g., self-testing in high income countries, schools, businesses, airports, venues). Finally, the **Economy Field** use case (with the electronics analogy "Flip phone") is the most constrained, as it includes tests used in field settings with a low operating costs (e.g., remote clinics, self-testing in LMICs, and global health applications). Keeping in mind these are use cases for POC diagnostics, in keeping with the consumer electronic analogy, complex diagnostics requiring laboratory infrastructure can be thought of as "Desktop computers".

For each use case, we will provide a description of the working environment and design considerations as see in the COVID-19 pandemic (**Figure 6C**), as well as provide examples of suitable technologies (**Figure 6D**). Additionally, we discuss how – as demand and utilization has increased for POC SARS-CoV-2 testing – testing volume has begun to shift from traditional POC testing sites in clinical settings (Premium Clinic and Economy Clinic) to decentralized field settings (Premium Field and Economy Field).

3.1 Premium Clinic

This use case encompasses settings with a moderate budget and clinical infrastructure. It is the least constrained use case for POC diagnostics, thereby easing design constraints and largely entails testing conducted at various parts of a hospital, like the emergency room, operating rooms, or ICU units. Here, trained personnel and resources such as electricity,

controlled ambient conditions, and refrigeration are present supporting the operation of more complex and less portable instruments. Price is not a major consideration giving the flexibility to purchase more expensive instruments. Moreover, speed is not an important consideration, as patients will typically spend longer periods of time receiving care at these settings.

For SARS-CoV-2 POC molecular testing, this use case is ideal for larger, more expensive benchtop instruments (tens of thousands of dollars) that may require a degree of laboratory skills for operation. During the pandemic, hospitals needed to triage patients suspected for COVID-19 into separate areas.[262] Some settings, like New York Presbyterian Hospital had already adopted industry standard POC molecular platforms like the Roche Cobas Liat, Cepheid GeneXpert, and BioFire FilmArray for other testing scenarios (e.g., Influenza), so they expanded testing on these platforms to quickly identify positive patients. These platforms, along with other near-patient molecular platforms have been evaluated across the country for use in various emergency, outpatient, and inpatient settings in hospitals.[263,264] Since, molecular testing is typically accessible here, antigen testing is typically not needed; however, with the extreme scenarios caused by the pandemic, some hospitals have implemented their use. For example, NHS in England recommends the use of COVID-19 LFAs to supplement PCR testing in the emergency department.[265] Finally, since antibody testing does not detect active infections, and rapid results are typically not needed, POC serology tests are not suited for this use case. Here, blood samples can be sent to a centralized laboratory for analysis.

In summary, the SARS-CoV-2 pandemic created an uptick in POC testing volumes in these settings. With hospitals purchasing more instruments to increase testing volumes, they have significantly expanded their testing capacities at the POC. Going forward, this may result in less testing being carried out in centralized laboratories and instead conducted in house.[266]

Additionally, rapid testing has been adopted in settings that typically wouldn't use them, which could open up the possibility for more rapid screening at hospitals of other infectious diseases, thus preventing their spread.

3.2 Economy Clinic

This use case represents clinical settings that are mainly constrained by costs (relative to the Premium Clinic use case). Here, trained personnel, along with access to external resources such as electricity and refrigeration may be present to run tests. Therefore, portability, full integration, may not be as critical, but cost is a major consideration. Finally, considerations for speed are important in the context of the length of patient visits, which can range from minutes to hours.

For SARS-CoV-2 testing, this use case is exemplified with testing in decentralized healthcare settings (e.g., urgent care clinics, pharmacies, physician offices). For example, CVS minute clinics around the U.S. have been providing rapid antigen or antibody tests.[267] Urgent care clinics like CityMD in NYC are also providing rapid testing on platforms like the BD Veritor plus. New clinics have also been set up, with the primary goal of providing COVID-19 testing. For example, NYC set up COVID Express sites around the city running the Cepheid GeneXpert Xpress platform.[268]

For molecular testing, platforms that were developed before the pandemic are particularly well suited for this use case (e.g., Abbott ID NOW or Mesa Biotech Accula). The instruments are relatively large and certain models can be low-cost enough (in the hundreds/thousands of dollars) to justify adoption in these settings. The key here is providing test results on site within a visit instead of sending samples to a centralized laboratory. For antigen testing, platforms like the Quidel Sofia 2 or BD Veritor plus are also well suited for this use case. The need for a benchtop

reader limits portability, but they provide a low-cost, rapid solution to testing. In fact, before the COVID-19 pandemic many of these decentralized healthcare settings already used these platforms for testing for respiratory infections or sexual health infections. Like in the Premium Clinic use case, these settings have increased their testing capacity by purchasing new instruments or adopting novel technologies.

3.3 Premium Field

The Premium Field use case allows for higher costs, but is constrained by supporting infrastructure to operate the test. With testing conducted outside of clinical settings, skilled operators or specialized equipment may not be available. As a result, the test must be self-contained, simple to operate, and portable. Price is an important but not predominant consideration, but speed is critical in order to give results in a timely manner.

Before the pandemic, this use case was largely restricted to self-testing in high income countries such as diabetes patients testing for glucose. The SARS-CoV-2 pandemic opened up the possibility of self-testing at home for infectious diseases as well as introduced new settings for testing such as schools, businesses, airports, or event venues. The development and commercialization of new technology targeted at this use case as well as growing acceptance and demand for consumer testing options has allowed for widespread infectious disease testing for the first time. For example, the Golden State Warriors of the NBA are providing all ticketed fans a Lucira Check It COVID-19 Test Kit to be tested at home before home games.[269] DoorDash launched a promotion to give restaurants discounted rapid antigen tests from Cellex (qSARS-CoV-2 Antigen Rapid Test) to screen employees and potentially customers.[270] The Los Angeles International Airport is providing travelers the Visby Medical test for $199.[271] Finally, England is

providing citizens with rapid tests twice a week, which is expected to allow citizens to get tests delivered to their homes, workplaces, and schools.[272]

With Cue Health and Lucira Health test kits now available OTC, consumers are able to run a nucleic acid test in the comfort of their own homes. Given the complexity and costs associated with molecular testing, many thought this was impossible before the pandemic. Now with the capacity to do so, consumer molecular testing opens many future avenues such as conducting serial laboratory quality testing for other widespread infectious diseases (e.g., respiratory conditions or sexually transmitted infections) in place of lower performing antigen tests. Additionally, this technology could expand the use of genetic testing and accelerate the adoption of personalized medicine.[273]

3.4 Economy Field

The Economy Field use case is the most constrained for POC diagnostics. It is constrained both by cost considerations (relative to field testing) as well as surrounding infrastructure to run the test (i.e., no specialized personnel, electricity, temperature/humidity control, or refrigeration). Therefore, portability, speed, costs, and simplicity are all important design considerations that must be taken into account. Traditionally, this use case has been synonymous with global health, where testing is done in the field in low- and middle-income countries. Without reliable access to many resources, and a need for low-costs, paper diagnostics have shined here, particularly the LFA. The LFA has provided many patients access to both low-cost antigen and antibody testing for various infectious diseases (e.g., malaria, HIV, Ebola) and there have been also been various efforts to transport the simplicity of the LFA for nucleic acid detection, as demonstrated in various academic research papers.[45,47] However, no such products have made it to commercialization.

In a way, the need for widespread COVID-19 testing has pushed this use case around the world. In order for individuals to conduct serial testing in any location it must be both easy to use, and cheap enough to justify adoption. For SARS-CoV-2 molecular testing, there currently is no developed solution that fits the criteria. Certain solutions like the Lucira Health test fit the technology needs, but the price is too high to be used in such scenarios ($55 a test). On other hand, rapid antigen and antibody testing is well suited for this use case. For example, the Abbott BinaxNOW test is a simple, low-cost solution and is currently being offered at pharmacies for ~$24 for 2 tests ($12 a test).[274] Additionally, various global health organizations have partnered to offer millions of rapid tests from Abbott and SD biosensor in low- and middle-income countries. For example, the Bill & Melinda Gates Foundation reached agreements with these manufacturers to offers tests at a maximum of $5 per test.[275] Note, the Abbott PanBio test uses the same assay chemistry as the BinaxNOW test, but is offered in a small cassette versus a card format and is authorized for use outside the U.S.[276]

With the COVID-19 pandemic spurring investment in low-cost POC diagnostics, various groups are looking to commercialize their molecular paper diagnostic technologies,[277] including with CRISPR diagnostics.

3.5 Discussion of POC uses cases during pandemic

The pandemic has forced centralized healthcare and decentralized healthcare settings to expand testing capacity. Throughout the pandemic, POC tests were increasingly adopted (**Figure 4B**), but the trends in POC usage for the three classes of assays were different.

1) For nucleic acid tests (**Figure 7**), the clinic use cases are dominant, as this is where POC molecular testing was largely conducted before the pandemic. There has been some headway into developing tests for field settings (Premium Field), but there remains a need for a

low-cost, portable nucleic acid testing option (Economy Field). As more nucleic acid tests are developed for home use, we expect prices to drop.

2) For antigen tests, the opposite is true, with a majority of tests suited for Economy Field settings. The antigen testing use case is inherently driven by the lack of economical and portable options for nucleic acid testing, so the advent of more nucleic acid testing technologies directed at the Premium Field and Economy Field use cases could pose significant competition to rapid antigen tests. However, further developments in signal readout methods for antigen tests, that improve sensitivity but maintain the simplicity of LFAs, could help maintain the popularity of LFA formats in field settings.

3) Finally, antibody tests are almost all geared towards Economy Field settings with the use of LFAs. Despite this intended use, significantly, there is currently no antibody test that has received EUA for home use or available OTC (**Figure 4B**). Possible reasons include lack of public health consensus in the use of such tests, and difficulties in offering POC collection of blood samples.

4. Conclusion and Future Directions

We used a holistic framework for the POC ecosystem to review developments during this unprecedented pandemic, focusing on points of interest – both technological and non-technological – to POC researchers and test developers. As the pandemic moves to a different phase, we discuss some possible trends.

Technology development trends. Across POC nucleic acid, antigen, and antibody tests, there have been many developments in assay chemistry (develop novel amplification methods, affinity reagents, and detection reagents) and microfluidics (which is increasingly being incorporated to automate assay steps and simplify operation of tests). Much effort has been made

to streamline the testing process with streamlined sample collection and processing. For instrumentation, capitalization on improved electronic and optical components is allowing for simpler, portable and lower cost instruments. Here, smart connected devices (especially smartphones) are being adopted as an important enhancement to the POC test. With increased digitization of healthcare, such tools will be integral in integrating with other data-centric health platforms, for test result reporting and data analysis.

Role of government. With investment in commercialization and deployment, we have seen that new POC diagnostics – including OTC tests – can be rapidly developed and deployed. However, we have also seen challenges in loosened regulation, with numerous POC antibody tests removed from the market, and – with increasing numbers of authorized platforms on the market – difficulty in comparing performance across different test platforms.

Apart from regulatory authorizations, government investments have been central in successfully pushing novel diagnostic technologies towards public use. Our analysis also suggests that while these investments led to deployment, they built on pre-existing and available technologies in a significant manner, and still required development time to tune the tests towards a novel target. In fact, the first at-home test was authorized for emergency use over a year into the pandemic. In a future disease outbreak, would we have the benefit of a similar lag time? Clearly, preparedness will be important. As the COVID-19 pandemic has illustrated, to rapidly direct POC tests towards new pathogens for diagnostics, surveillance, and analysis requires a thorough and comprehensive effort. It will be important to create the workflows and testing and data infrastructure to support future widespread testing. While government investment in commercialization efforts was critical during an emergency, it will be critical to

continue investment in the development of novel technologies in anticipation of new infectious-disease challenges and public health needs.

POC use cases. Early into the pandemic, SARS-CoV-2 testing was limited to select sites, which decreased overall access and even endangered public health by promoting crowded conditions. Over a year into the pandemic, workflows and data infrastructure are being built across different POC settings to support POC COVID-testing for all assay types, especially nucleic-acid testing and increasingly antigen and antibody tests. There is continued development and expansion of assays for home use. Whereas all four described POC use cases were being met with diagnostic technologies, the trend towards field testing – which has been occurring in this pandemic – will likely persist into the future for infectious-disease diagnostics and more broadly, a next phase for digital, personalized, and preventive medicine.

POC diagnostics and digital health. The COVID-19 pandemic has demonstrated that POC diagnostics, including OTC testing, is feasible and increasingly accepted by healthcare workers and the public. Moving forward, there will undoubtedly be continued interest in coronavirus testing as well as other respiratory illnesses, and it remains to be seen how much POC testing will expand to other applications, including to services currently requiring high-complexity techniques such as personalized genetic testing and liquid biopsy for cancer detection. While a number of technical developments are still required in order to make high-complexity tests (especially nucleic acid diagnostics) widely available at a low cost, it remains to be seen whether the increasing availability of POC tests will merely shift testing away from centralized laboratories, or spur growth in overall testing and monitoring towards a different paradigm for health and medicine that is digital, personalized and preventive. While that is an open question, it is worthwhile to recognize how academia, government, and industry responded

to successfully develop and deploy POC diagnostic technologies with unprecedented pace, and never before has the public been so interested or invested in POC diagnostics.

Author Contributions

Harshit Harpaldas, Siddarth Arumugam, Chelsey Campillo Rodriguez, Bhoomika Ajay Kumar, Vivian Shi, and Samuel K. Sia all contributed to the writing, reviewing, and editing of this manuscript.

Conflicts of Interest

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Tables

Table 1: Technology map of design choices made by selected SARS-CoV-2 POC Diagnostics

POC Test	Assay Chemistry	Microfluidics								Connected Instrument
		Material	Reagent Storage	Sample Type	Sample Processing	Fluid Actuation	Fluid Control	Fluid Mixing	Signal Detection	
Cue Health	Isothermal	Plastic	Dry reagents	Nasal Swab	Target binding with affinity molecules	Capillary	Wax valves	Active (sonication)	Electrochemical	Portable, Bluetooth connected reader (Cue Cartridge Reader) Cue Health mobile app
Lucira Health	Isothermal (RT-LAMP)	Plastic	Dry reagents (in test unit)	Nasal Swab	Lysis (in vial)	N/A	Reaction chambers	Manual/ Passive	Colorimetric	Optical reader, mobile app (LUCI pass)
Visby Medical	RT-PCR	Plastic	Dry reagents (on chip)	Nasal Swab	Lysis (on-chip)	Gear motor	Rotary (on-chip) valves	Passive	Colorimetric (LFA)	None
Mesa Biotech	RT-OSCAR	Plastic, Paper	Dry reagents (on-chip)	Nasal Swab	Lysis (on-chip)	Pneumatic/ Capillary	Patented passive fluid flow technology	Passive	Colorimetric (LFA)	None
Cepheid Xpert Omni	RT-PCR	Plastic	Dry Reagents (on-chip)	Nasal/nasopharyngeal/ throat swab	Lysis/ extraction (on-cartridge)	Pneumatic	Rotary valves	Passive	Fluorescence	Portable, Bluetooth connected
Abbott ID NOW	Isothermal (NEAR)	Plastic	Dry reagents	Nasal/nasopharyngeal/ throat swab	Lysis (off-chip)	Manual	Manual	Manual	Fluorescence	Portable instrument with LCD screen
Minute Molecular DASH	RT-qPCR	Plastic, thin film	Dry reagents (on-cartridge)	Nasal/nasopharyngeal swab, saliva	Lysis/ Paramagnetic particle extraction (on-cartridge)	Capillary	Passive	Passive	Fluorescence	Barcode scanner, cloud connectivity
Talis One	Isothermal	Plastic	Dry reagents	Nasal/oral swab	Solid-phase extraction	SlipChip	Passive	Passive	Fluorescence	Portable instrument,

					and purification (on-cartridge)					cloud connectivity
Nuclein Hand-Held PCR test	RT-qPCR	Plastic	Dry reagents	Saliva	Lysis/extraction (in chamber)	Magnetic displacer piston	Passive	Passive	Fluorescence	On-board LCD screen
Roche Cobas Liat	RT-PCR	Plastic	In assay tube	Nasopharyngeal or Nasal Swab	Extraction and purification (in vial)	Pneumatic	Passive	Passive	Fluorescence	Portable instrument with LCD screen and barcode scanner
Ellume	LFA	Paper	In tube and dry reagents on strip	Nasal Swab	Mix with processing fluid – contains fluorophore (off-strip)	Capillary	Passive	Passive	Fluorescence (LFA)	Integrated optical reader (eStick)
LumiraDx	Microfluidic immunofluorescence assay	Plastic	Dry reagents (on-strip)	Nasopharyngeal swab	Lysis (off-strip)	Capillary /Pneumatic	Passive	Active	Fluorescence	Portable, connected reader
Luminostics ClipCOVID	LFA	Paper	Dry reagents (on-strip)	Nasal swab	Lysis (off-strip)	Capillary	Passive	Passive	Luminescence (LFA)	Portable analyzer with mobile app (Clip COVID app)
Abbott BinaxNOW	LFA	Paper	Dry reagents (on-strip)	Nasal swab	Lysis (on-test card)	Capillary	Passive	Passive	Colorimetric (LFA)	Mobile app to record results (NAVICA)
LightDeck	Fluorescence immunoassay	Plastic	Dry reagents (on-chip)	Nasal swab (antigen) / Serum (antibody)	Lysis (off-chip)	Capillary	Passive	Passive	Fluorescence (planar waveguide technology)	Portable, connected instrument

Qorvo Omnia	Microfluidic immunoassay	Plastic	On Chip	Nasal swab	Lysis (off-chip)	Pneumatic	Passive	Passive	Bulk Acoustic Wave	Instrument with touchscreen
Celltrion Sampinute (with BBB)	Magnetic force-assisted electrochemical sandwich immunoassay (MESIA)	Plastic	Reagent Solution (off-chip)	Nasopharyngeal swab	Mix with Reagent Solution tube (off-chip)	Magnetic	N/A	N/A	Electrochemical	Instrument with touchscreen
Nanomix eLab	Carbon nanotube electrochemical immunoassay	Plastic	On chip	Nasal Swab	N/A	Pneumatic	Diaphragm valves	Active	Electrochemical	Portable instrument with touchscreen
NOWdiagnostics ADEXUSDx	LFA	Paper	Dry reagents (on-strip)	Fingerstick whole blood	Plasma separation (on membrane)	Capillary	Passive	Passive	Colorimetric (LFA)	ADEXUSDx Analyzer or DxREADER
AssureTech Assure Rapid Test	LFA	Paper	Dry reagents (on-strip)	Fingerstick whole blood (POC) or serum/plasma	N/A	Capillary	Passive	Passive	Colorimetric (LFA)	N/A
QIAGEN QIAreach	LFA	Paper	In tube and dry reagents on strip	Serum/Plasma	Mix with processing fluid – contains fluorophore (off-cartridge)	Capillary	Passive	Passive	Fluorescence (LFA)	Optical reader (estick), connected to eHub

Table 2: Selected POC diagnostics for SARS-CoV-2 nucleic acid detection. All tests selected here have received US Federal funding (Figure 5)

Company	Product	Applications beyond SARS-CoV-2	Technology highlight for POC use	Authorization	Year company founded
Cue Health	COVID-19 Test	Respiratory, Sexual Health (Under development)	Portable reader with smartphone connectivity, 20 min TAT	FDA EUA - POC/Home/ OTC	2010
Lucira Health	Check It COVID-19 Test Kit	Influenza (Under development)	Colorimetric detection with low-cost reader	FDA EUA - POC/Home/ OTC	2013
Visby Medical	COVID-19 Test	Influenza A/B, CT/NG/TV, AMR (Under development)	Single-use, disposable RT-PCR test	FDA EUA - POC	2012
Mesa Biotech	Accula SARS-CoV-2	Influenza A/B, RSV	Low-cost instrument, LFA readout	FDA EUA - POC	2015
Cepheid	Omni SARS-CoV-2	TB, HIV, Ebola	Portable, battery powered version of GeneXpert system	FDA EUA - POC	1996
QIAGEN	QIAstat-Dx Respiratory SARS-CoV-2 Panel	Respiratory panel	Syndromic testing panel (21 targets)	FDA EUA	2010
Minute Molecular	DASH	Respiratory (Influenza A/B), Sexual health (HCV, CT/NG/TV)	Portable, multiplex qPCR with TAT < 15 minutes	Under development	2017
MatMaCorp	COVID-19 2SF Test	Agriculture	Portable, low-cost, batch testing	FDA EUA	2014

Talis Biomedical	Talis One	Respiratory (Influenza A/B), Sexual and Women's Health (CT/NG/Mgen /Trich, HSV, UTI, BV, GBS)	Single-use cartridge, automated sample-to-answer, cloud connectivity	Under development	2010
Nuclein	Hand-Held PCR Test	Zika	Small, battery-powered, disposable, real-time PCR	Under development	2017
MicroGEM	Spitfire 6830 SARS-CoV-2	N/A	Multiplexed microfluidic cartridge with 15 min TAT	Under development	2015
Tangen Biosciences	GeneSpark	Respiratory, bloodstream infection (bacterial and AMR), candida auris	Portable device for isothermal amplification and multiplexing up to 32 targets	Under development	2013
Ubiquitome	Liberty16	N/A	16 samples in 40 min, compact, smartphone-controlled PCR machine	Under development	2014

Table 3: Selected POC diagnostics for SARS-CoV-2 antigen detection

Company	Product	Applications beyond SARS-CoV-2	Technology highlight for POC use	Authorization	Year company founded
BD	Veritor Plus	Influenza A/B, Group A Strep, RSV	Portable reader, LFA	FDA EUA - POC	1897
Quidel	Sofia 2	Influenza, RSV, Strep A Lyme, hCG, Legionella, Vitamin D	Portable reader, fluorescence LFA	FDA EUA - POC	1981
Ellume	COVID-19 Home Test	Influenza, TB	Disposable, connected reader for fluorescence LFA	FDA EUA - POC/Home/ OTC	2010
LumiraDx*	SARS-CoV-2 Ag Test	D-dimer, INR	Microfluidic test strip and portable reader	FDA EUA- POC	2014
Abbott	BinaxNOW	Influenza A/B, RSV, Malaria	Low-cost, no reader required	FDA EUA - POC/Home/ OTC	1991
Luminostics	ClipCOVID	N/A	Smartphone adapter for LFA readout	FDA EUA - POC	2014
Nanomix*	Elab	Sepsis	Handheld reader, carbon nanotube detection	EUA request under review	2000
Maxim Biomedical	SARS-CoV-2 Rapid Antigen Test	HIV	Visual readout, no reader required	Under development	2005
Hememics*	ChipLab	Hospital acquired infections (HAIs)	Portable, graphene based multiplex sensor (17 targets) with 1 min TAT	Under development	2009

Orasure	COVID-19 rapid antigen test	Influenza A/B, HCV, HIV, Ebola	Saliva sample	EUA request under review	1987

**Developing an antigen and antibody test for SARS-CoV-2*

Table 4: Selected POC diagnostics for SARS-CoV-2 antibody detection

Company	Product	Applications beyond SARS-CoV-2	Technology highlight for POC use	Authorization	Year company founded
InBios International*	SCov-2 Ab Detect Rapid Test	Infectious disease	Lateral flow	Under development	1996
NOWDiagnostics	ADEXUSDx COVID-19 Test	HIV, troponin, hcG, Acetaminophen, H-FABP, Methanol Dip, Salicylate	Integrated capillary for blood collection	FDA EUA - POC	2014
LightDeck*	COVID-19 Antibody Test	Hormones, Host Response, Cardiac Markers, Water Testing, Veterinary	Planar waveguide technology with disposable test cartridges	Under development	2009
AssureTech**	COVID-19 IgG/IgM Rapid Test	Cardiac, pregnancy, infectious disease, tumor, drugs of abuse allergy	Lateral flow	FDA EUA - POC	2008
JoysBio**	COVID-19 Neutralizing Antibody Test Kit	Cardiac, pregnancy, infectious disease, tumor, drugs of abuse	Neutralizing antibody LFA	CE-IVD	2010
Nirmidas Biotech**	Midaspot COVID-19 Antibody Combo Detection Kit	N/A	Lateral flow	FDA EUA - POC	2013
QIAGEN** (with Ellume)	QIAreach Anti-SARS-CoV-2 Total Test	TB	Estick technology with ehub to run multiple tests	FDA EUA	1984

*Developing an antigen and antibody test for SARS-CoV-2
** Did not receive US Federal support

Figure Legends

Figure 1. Overview of the POC diagnostics ecosystem in a pandemic age. All technology and non-technology components play a role in determining the systems integration (i.e., use case) of POC diagnostic devices. Adapted from reference 2 with permission from American Chemical Society.

Figure 2. Images of selected industry examples of SARS-CoV-2 POC tests. Nucleic acid tests (A-C), antigen tests (D-F), antibody tests (G-I). A) Lucira Health CHECK-IT COVID -19 Test. Adapted from reference 278 with permission from Elsevier.[278] B) Visby Medical COVID-19 Point-of-Care Test. Taken from www.visbymedical.com with permission from Visby Medical C) Cue Health Cue COVID -19 Test. Taken from www.cuehealth.com with permission from Cue Health D) Ellume COVID-19 Home Test. Credit to Ellume E) Luminostics Clip COVID Rapid Antigen Test. Credit to Luminostics. Inc. F) LumiraDx SARS-CoV-2 Ag Test. Credit to LumiraDx G) Assure Tech Assure COVID-19 IgG/IgM Rapid Test Device. Credit to Assure Tech. H) NOW Diagnostics ADEXUSDx COVID-19 Test. Adapted from reference 279 with permission from Elsevier.[279] I) JoysBio SARS-CoV-2 IgG/Neutralizing Antibody Rapid Test Kit. Taken from en.joysbio.com with permission from JoysBio.

Figure 3. Timeline of OTC tests approved by the FDA from 1990 to 2020. Data from FDA's OTC database

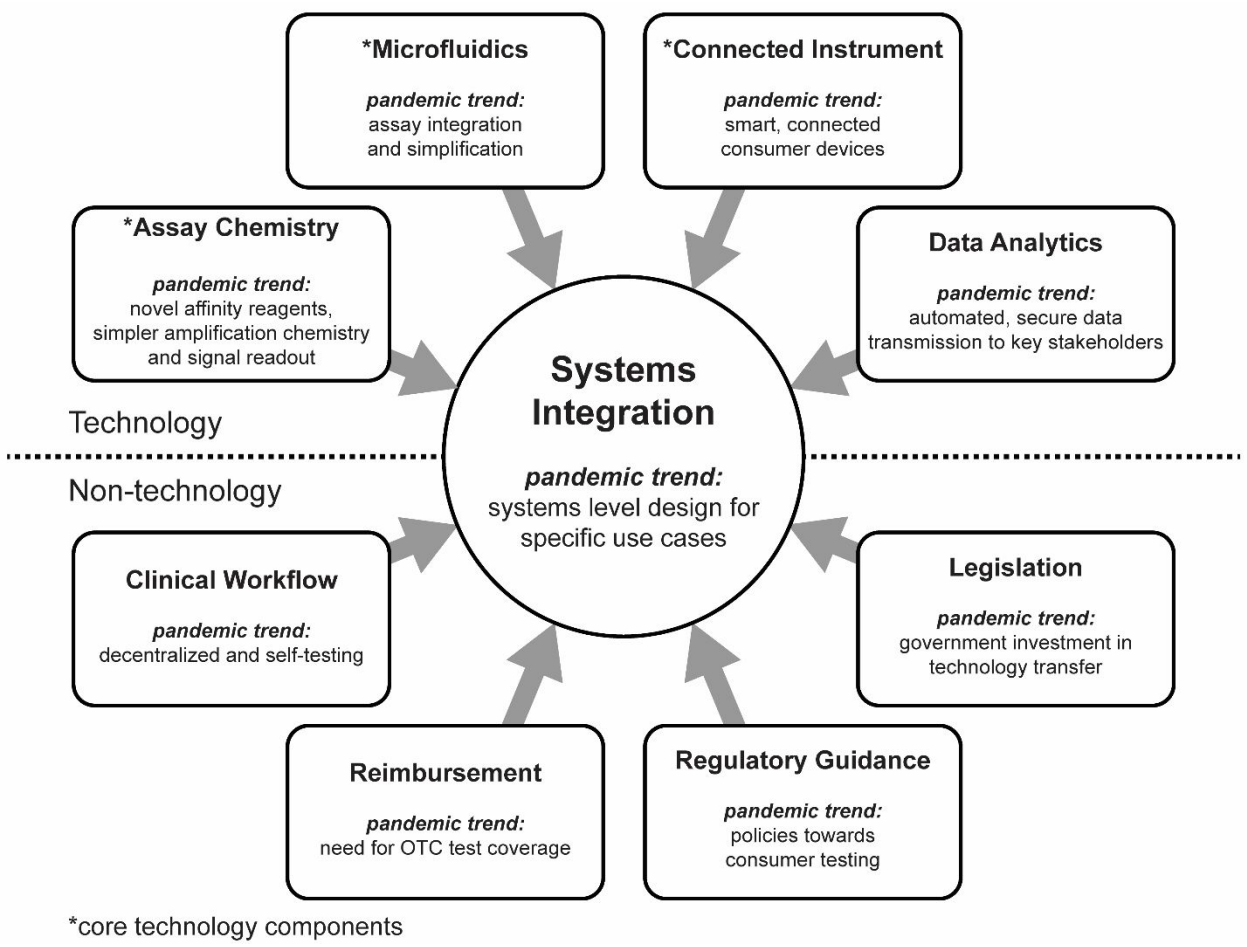
Figure 4. Overview of IVD's that have received FDA EUA A) Total number of IVD's issued EUA by the FDA during previous declarations of the EUA pathway. **Note**: IVD's that have had their EUA revoked are included in the analysis, and all listed pathogens here have current EUAs except H1N1 (designated with *). B) Breakdown of current SARS-CoV-2 IVDs that have received EUA by assay type (nucleic acid, antigen, antibody) and authorized setting to run the test. See ESI for more information on methods for data compilation.

Figure 5. Unofficial chart demonstrating relationships between company history, government funding (NIH, BARDA, DoD), and time to first EUA. A) Year of company founding versus time (months) to company's initial FDA EUA from declaration of public health emergency on February 4th, 2020. B) Year of company founding versus US Federal funding in millions of dollars C) US Federal funding versus time to initial FDA EUA from declaration of public health emergency. **Note:** The date of company founding for Abbott uses the founding date of Alere, which originally developed the POC technologies (BinaxNOW and ID NOW) and was acquired by Abbott in 2017**.** See ESI for more information on methods for data compilation and **Supplementary Table 3** for specific tests included in the analysis.

Figure 6: POC use cases, decoupling cost from infrastructure. A) Graphical representation of uses cases in 2x2 grid, with each use case assigned a representative color, and icon describing example settings B) Graphical representation of use cases using consumer electronics analogy C) General description and main design considerations for each use case D) Examples of SARS-CoV-2 POC diagnostics ideal for each use case (based on technology). Adapted from reference 2 with permission from American Chemical Society. This figure has been designed using icons made by Freepik, Eucalyp, and xnimrodx from Flaticon.com.

Figure 7: Breaking down the POC diagnostic platforms that have received FDA EUA by their use case. **Note:** platforms with multiple tests approved (e.g., for SARS-CoV-2 and panel including Influenza/RSV) were only counted once in this analysis. Use case analysis was based on ideal fit for underlying technology with **Supplementary Table 4** outlining the specific tests included in each category. Cepheid GeneXpert was counted for both centralized and decentralized healthcare due to various instrument sizes available.

Figure 1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pandemic trend:
assay integration
and simplification
*Connected Instrument
pandemic trend:
smart, connected
consumer devices
*Assay Chemistry
pandemic trend:
novel affinity reagents,
simpler amplification chemistry
and signal readout
Data Analytics
pandemic trend:
automated, secure data
transmission to key stakeholders
Systems Integration
pandemic trend:
systems level design for
specific use cases
Technology
Non-technology
Clinical Workflow
pandemic trend:
decentralized and self-testing
Legislation
pandemic trend:
government investment in
technology transfer
Reimbursement
pandemic trend:
need for OTC test coverage
Regulatory Guidance
pandemic trend:
policies towards
consumer testing
*core technology components

Figure 2


A
LUCIRA
Ready Done
COVID-19
Positive
Negative
B
visby medical
COVID-19
RESULTS VALID
POSITIVE for SARS-CoV-2 (COVID-19)
1
2
3
C
COVID-19 Negative
D
Your test is POSITIVE for COVID-19
E
Negative
F
G
AB 347
C
IgG
IgM
S
H
ADEXUSDx®
COVID-19
C
T
Control Line
Test Line
Fill Line
Fill Zone
Sample Application Zone
I
C — Control Line
1 — IgG Antibody
2 — Neutralizing Antibody

Figure 3

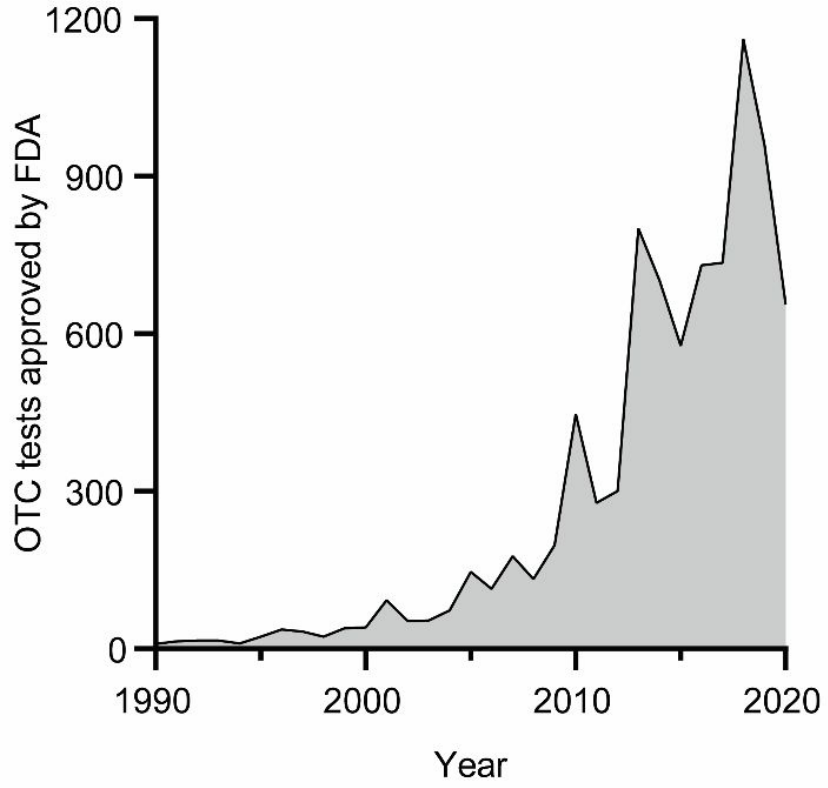

1200
900
600
300
0
OTC tests approved by FDA
1990
2000
2010
2020
Year

Figure 4

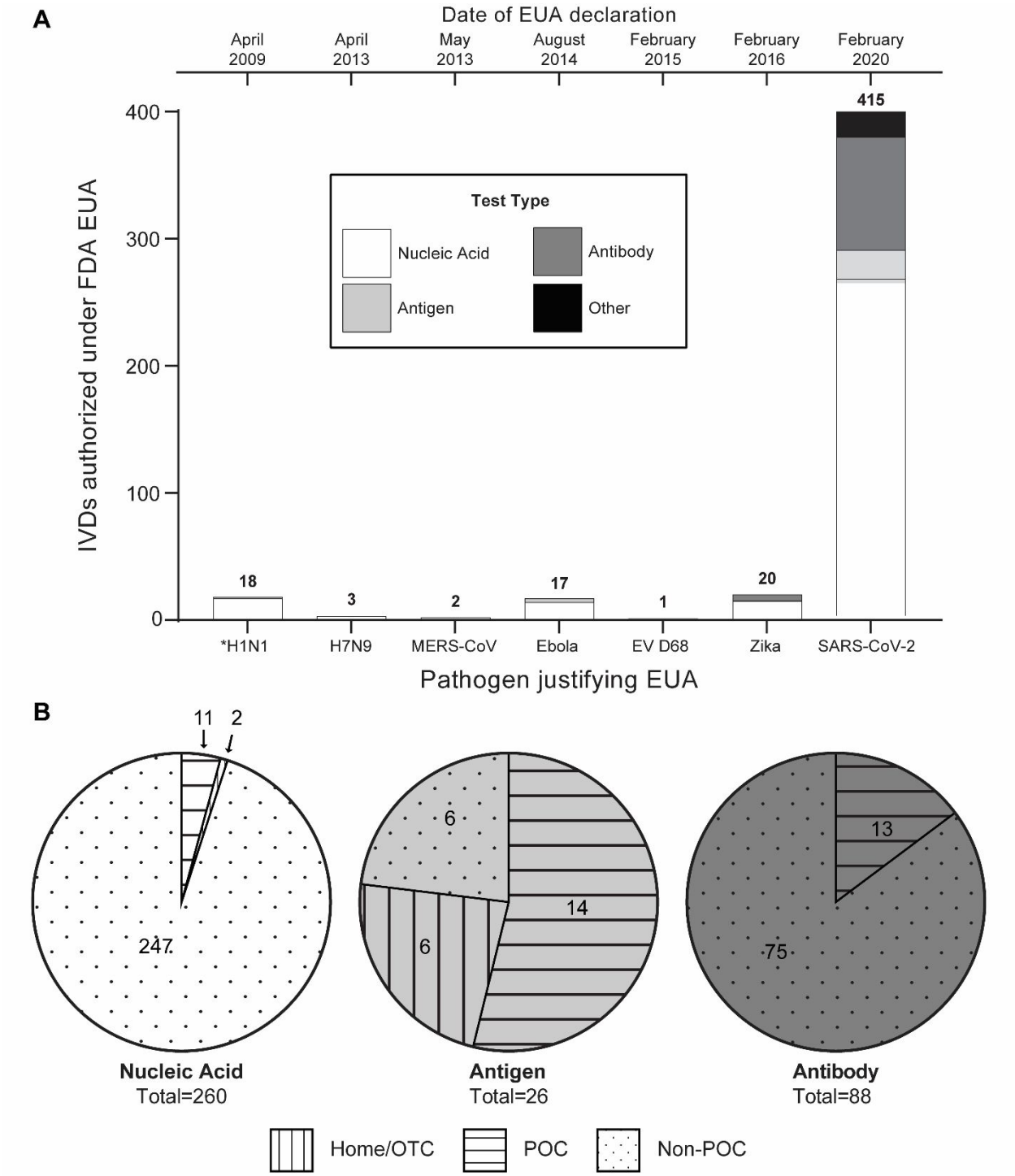

A
Date of EUA declaration
April 2009
April 2013
May 2013
August 2014
February 2015
February 2016
February 2020
IVDs authorized under FDA EUA
400
300
200
100
0
Test Type
Nucleic Acid
Antibody
Antigen
Other
18
3
2
17
1
20
415
*H1N1
H7N9
MERS-CoV
Ebola
EV D68
Zika
SARS-CoV-2
Pathogen justifying EUA
B
11
2
247
6
6
14
13
75
Nucleic Acid
Total=260
Antigen
Total=26
Antibody
Total=88
Home/OTC
POC
Non-POC

Figure 5

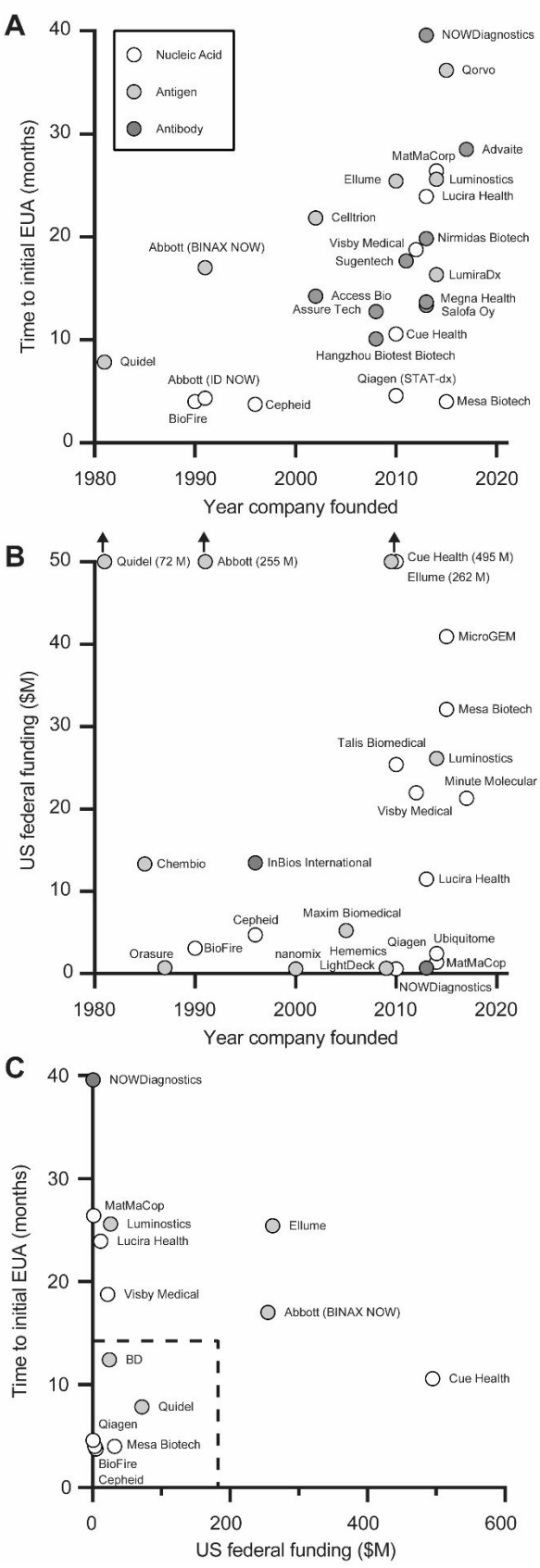

A
Nucleic Acid
Antigen
Antibody
Time to initial EUA (months)
Year company founded
NOWDiagnostics
Qorvo
Advaite
MatMaCorp
Ellume
Luminostics
Lucira Health
Celltrion
Nirmidas Biotech
Visby Medical
Abbott (BINAX NOW)
Sugentech
LumiraDx
Access Bio
Assure Tech
Megna Health
Salofa Oy
Cue Health
Hangzhou Biotest Biotech
Quidel
Abbott (ID NOW)
Qiagen (STAT-dx)
Cepheid
Mesa Biotech
BioFire
B
US federal funding ($M)
Year company founded
Quidel (72 M)
Abbott (255 M)
Cue Health (495 M)
Ellume (262 M)
MicroGEM
Mesa Biotech
Talis Biomedical
Luminostics
Minute Molecular
Visby Medical
Chembio
InBios International
Lucira Health
Maxim Biomedical
Cepheid
Qiagen
Ubiquitome
Orasure
BioFire
nanomix
Hememics
LightDeck
MatMaCop
NOWDiagnostics
C
Time to initial EUA (months)
US federal funding ($M)
NOWDiagnostics
MatMaCop
Luminostics
Lucira Health
Ellume
Visby Medical
Abbott (BINAX NOW)
BD
Cue Health
Quidel
Qiagen
Mesa Biotech
BioFire
Cepheid

Figure 6

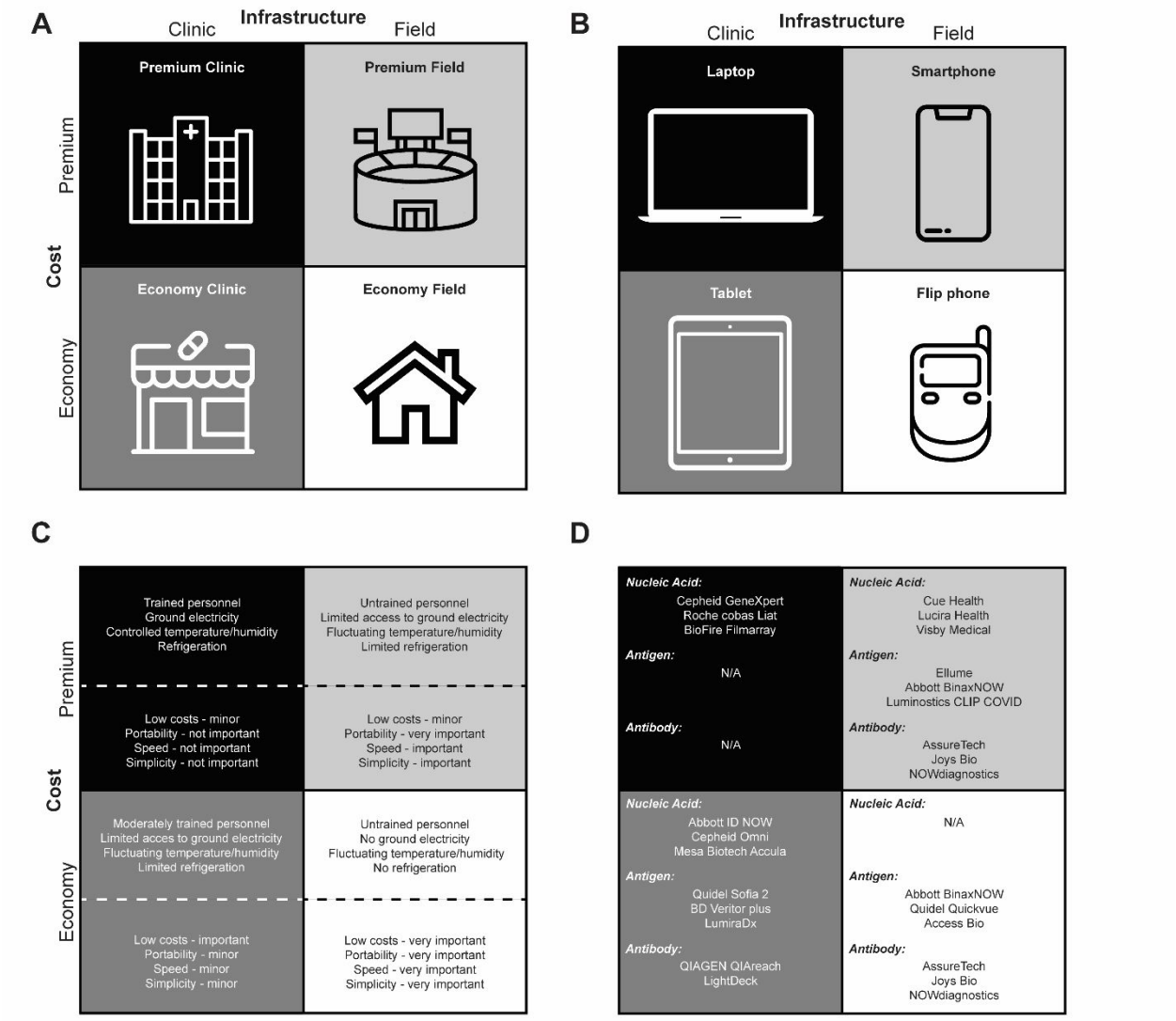
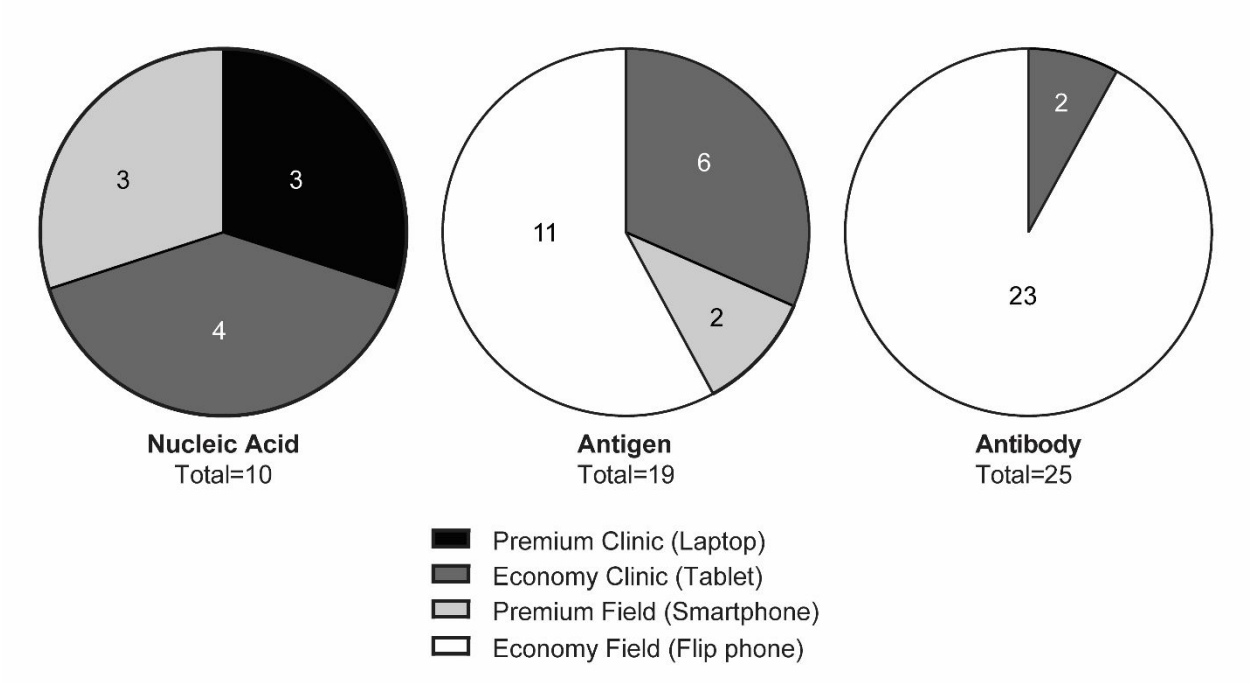

A
Infrastructure
Clinic
Field
Cost
Premium
Economy
Premium Clinic
Premium Field
Economy Clinic
Economy Field
B
Infrastructure
Clinic
Field
Laptop
Smartphone
Tablet
Flip phone
C
Cost
Premium
Economy
Trained personnel
Ground electricity
Controlled temperature/humidity
Refrigeration
Untrained personnel
Limited access to ground electricity
Fluctuating temperature/humidity
Limited refrigeration
Low costs - minor
Portability - not important
Speed - not important
Simplicity - not important
Low costs - minor
Portability - very important
Speed - important
Simplicity - important
Moderately trained personnel
Limited acces to ground electricity
Fluctuating temperature/humidity
Limited refrigeration
Untrained personnel
No ground electricity
Fluctuating temperature/humidity
No refrigeration
Low costs - important
Portability - minor
Speed - minor
Simplicity - minor
Low costs - very important
Portability - very important
Speed - very important
Simplicity - very important
D
Nucleic Acid:
Cepheid GeneXpert
Roche cobas Liat
BioFire Filmarray
Antigen:
N/A
Antibody:
N/A
Nucleic Acid:
Cue Health
Lucira Health
Visby Medical
Antigen:
Ellume
Abbott BinaxNOW
Luminostics CLIP COVID
Antibody:
AssureTech
Joys Bio
NOWdiagnostics
Nucleic Acid:
Abbott ID NOW
Cepheid Omni
Mesa Biotech Accula
Antigen:
Quidel Sofia 2
BD Veritor plus
LumiraDx
Antibody:
QIAGEN QIAreach
LightDeck
Nucleic Acid:
N/A
Antigen:
Abbott BinaxNOW
Quidel Quickvue
Access Bio
Antibody:
AssureTech
Joys Bio
NOWdiagnostics

Figure 7


3
3
4
Nucleic Acid
Total=10
6
11
2
Antigen
Total=19
2
23
Antibody
Total=25
Premium Clinic (Laptop)
Economy Clinic (Tablet)
Premium Field (Smartphone)
Economy Field (Flip phone)

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Electronic Supplementary Information (ESI) for:

Point-of-Care Diagnostics: Recent Developments in a Pandemic Age

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Data acquisition methods for figures in main text:

Figure 3:

Data on the number of over-the-counter (OTC) test approvals from 1990 to 2020 was obtained from the U.S Food and Drug Administration (FDA) Over the Counter database.[1] Data was collected for each year individually, by setting the effective date from January 1st to December 31st, exporting search results to a spreadsheet, and enumerating the list.

Figure 4:

All data in this figure was acquired as of September 26, 2021.

For Figure 4A, data on in vitro diagnostics (IVDs) that received emergency use authorization (EUA) in previous public health emergencies was compiled from the FDA website. Information on the current EUAs in place and the tests authorized for each can be found here.[2,3] Information on IVDs that have had their EUA revoked, including tests developed for H1N1 influenza (no current EUA in place), can be found here.[4] Tests were compiled and grouped under assay type (nucleic acid, antigen, antibody) in Microsoft Excel 2019, and graphed in GraphPad Prism 9. The "Other" category for SARS-CoV-2 IVDs includes laboratory developed nucleic acid tests, T-cell tests, and IVDs for management of COVID-19 patients (3 tests detecting Interleukin-6).[5]

For Figure 4B, data on current EUAs for SARS-Cov-2 IVDs was compiled from FDA databases covering the three main assay types (nucleic acid[6], antigen[7], antibody[8]). Data on the authorized setting was also compiled from the same databases. Non-POC designates tests authorized to be utilized in laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, that meet requirements to perform high and moderate complexity tests (H,M). Tests that are categorized as N/A were also included in this category (e.g., collection kits). POC designates tests authorized to be utilized in patient care settings operating under a CLIA Certificate of Waiver (W). Home/OTC designates tests authorized for home-use and available OTC. Note, the home and OTC categories are grouped together as all tests currently approved for home-use are also available OTC. Additionally, all tests were categorized by their most restricted authorized setting, and only tests on the same platform that detect another target (e.g., includes Influenza) were counted more than once in the analysis. All data was compiled in Microsoft Excel 2019 and graphed in GraphPad Prism 9. For more information on the tests included in each category see **Supplementary Table 3.**

Figure 5:

All data in this figure was acquired as of July 15, 2021.

Data on the company founding date was collected from various web searches on google.com. In order to obtain the time (in months) for each company to receive an initial EUA from the FDA, the dates for the company's first FDA EUA were recorded using the FDA databases.[6–8] The time from the initial declaration of the EUA pathway by the FDA (February 4th, 2020) was then calculated and utilized in the analysis. Information on US federal funding was restricted to three sources, National Institutes of Health (NIH) Rapid Acceleration of Diagnostics (RADx)

initiative, Biomedical Advanced Research and Development Authority (BARDA), and the Department of Defense (DoD). For RADx, and BARDA numbers were taken from their respective websites which list funding given to various companies during the COVID-19 pandemic.[9,10] Information on DoD funding was obtained from various press releases from both the DoD and individual companies. Data was collected, and aggregated in Microsoft Excel 2019 and plotted using GraphPad Prism 9.

Figure 7:

All data in this figure was acquired as of September 26, 2021.

Using the FDA databases on IVDs that received EUA,[6–8] POC diagnostic platforms were grouped based on their use case (described in main text). The analysis done here was based solely on the platform, therefore platforms with multiple tests were only included once in the analysis. See **Supplementary Table 4** for a breakdown of the tests included in each category.

Supplementary Tables:

Supplementary Table 1: Company reported performance metrics for POC nucleic acids tests discussed in main text:

Test Name	Sensitivity (95% CI)	Specificity (95% CI)	Sample Type	Reported Limit of Detection (LOD)	Sample Type	LOD with FDA Reference Panel
Abbott ID NOW COVID-19	100% (83.9 -100%)	100% (88.7 -100%)	Contrived NP swabs	125 genome equivalents/mL	Purified RNA diluted in NP matrix	$3x\ 10^5$ NDU/mL
Mammoth Biosciences SARS-CoV-2 DETECTR kit	95% (83.5 - 98.6%)	100% (94.2 -100%)	Clinical NP swabs (prospective)	20 copies/µL (20,000 copies/mL)	AccuPlex Verification Panel Reference material diluted in NP matrix	$5.4x\ 10^5$ N DU/mL
Sherlock Biosciences Sherlock CRISPR SARS-CoV-2 kit	100% (83.9 -100%)	100% (88.6 -100%)	Contrived NP swabs	6.75 copies/µL (6,750 copies/mL)	Extracted RNA diluted in NP matrix	$0.6x10^4$ NDU/mL
Mesa Biotech Accula SARS-CoV-2 Test	95.8% (78.9 -99.9%)	100% (86.7 -100%)	Clinical nasal swabs (retrospective)	150 copies/mL	Heat inactivated virus diluted in nasal matrix	$4.75x\ 10^2$ NDU/mL
Visby Medical COVID-19 Point of Care Test	100% (89.0 -100%)	95.30% (87.1 -98.4%)	Clinical NP swabs (prospective)	435 copies/swab	Inactivated virus diluted in NP matrix	$5.4x\ 10^4$ NDU/mL
Roche cobas liat SARS-CoV-2 & Influenza A/B	100% (93.6 -100%)	100% (98.4 -100%)	Clinical NP swabs (prospective)	12 copies/mL	Heat inactivated virus diluted in NP matrix	$5.4x\ 10^3$ NDU/mL
Lucira Health CHECK-IT COVID-19 Test Kit	91.7% (85.6 - 95.8%)	98.2% (95.8 - 99.4%)	Clinical nasal swabs (prospective)	2700 copies/swab (900 copies/mL)	Heat inactivated virus diluted in nasal matrix	N/A
Cue Health COVID-19 Test	97.4% (86.5 -99.5%)	99.1% (96.9 – 99.8%)	Clinical nasal swabs (prospective)	1.3 genome copies/µL (1,300 copies/mL)	Viral RNA diluted in nasal matrix	$6\ x\ 10^4$ NDU/mL (Dry Swab)
Cepheid Xpert Xpress SARS-CoV-2	97.8% (88.4 – 99.6%)	95.6% (85.2 – 98.8%)	Clinical NP swabs (retrospective)	0.02 PFU/mL	Live virus diluted in NP swab matrix	$5.4x\ 10^3$ NDU/mL

BioFire Filmarray Respiratory Panel 2.1-EZ	98.40% (91.4 - 99.7%)	98.9% (97.5 – 99.5%)	Clinical NP swabs (prospective)	500 copies/mL	Heat inactivated virus diluted in NP swab matrix	6.0x 10^3 NDU/mL
Cepheid Omni SARS-CoV-2	97.6% (91.5 - 99.3%)	99.1% (94.8 - 99.8%)	Clinical NP swabs (prospective)	400 copies/mL	Heat inactivated virus diluted in NP swab matrix	N/A

Note: All performance metrics were obtained from Instruction for Use (IFU) documents from FDA EUA database. NDU stands for RNA NAAT detectable units and is further defined here on the FDA website.[11]

Supplementary Table 2: Company reported performance metrics for POC antigen tests discussed in main text:

Test Name	Sensitivity (95% CI)	Specificity (95% CI)	Sample Type	Reported Limit of Detection (LOD)	Sample Type
Quidel Sofia SARS Antigen FIA	96.70% (83.3 - 99.4%)	100% (97.9 -100%)	Clinical nasal swabs (prospective)	$1.13x10^2$ $TCID_{50}$/mL	Heat inactivated virus diluted in nasal swab matrix
Quidel QuickVue At-Home COVID-19 Test	83.5% (74.9 - 89.6%)	99.2% (97.2 -99.8%)	Clinical nasal swabs (prospective)	$1.91x10^4$ $TCID_{50}$/mL	Heat inactivated virus diluted in nasal swab matrix
Abbott BinaxNOW COVID-19 Ag Card Home Test	91.7% (73.0 - 98.9%)	100% (87.7 - 100.0%)	Clinical nasal swabs (prospective)	140.6 $TCID_{50}$/mL	Heat inactivated virus diluted in nasal swab matrix
Ellume COVID-19 Home Test	95% (82 - 99%)	97% (93 - 99%)	Clinical nasal swabs (prospective)	$10^{3.8}$ (6,310) $TCID_{50}$/mL	Heat inactivated virus diluted in NP swab matrix
Luminostics CLIP COVID Rapid Antigen Test	96.9% (83.8 - 99.9%)	100% (97.3 – 100%)	Clinical nasal swabs (prospective)	0.88×10^2 $TCID_{50}$/mL	Gamma irradiated virus diluted in nasal swab matrix
LumiraDx SARS-CoV-2 Ag Test	97.6% (91.6 - 99.3%)	96.6% (92.7 - 98.4%)	Clinical NP swabs (prospective)	32 $TCID_{50}$/mL	Gamma irradiated virus diluted in nasal swab matrix
BD Veritor System for Rapid Detection of SARS-CoV-2	84% (67 - 93 %)	100% (98 -100%)	Clinical nasal swabs (prospective)	$1.4x10^2$ $TCID_{50}$/mL	Gamma irradiated virus diluted in nasal swab matrix
BD Veritor At-Home COVID-19 Test	84.6% (70.3 - 92.8%)	99.8% (99 - 100%)	Clinical nasal swabs (prospective)	$1.87x10^5$ $TCID_{50}$/mL	Gamma irradiated virus diluted in nasal swab matrix

Note: All performance metrics were obtained from Instruction for Use (IFU) documents from the FDA EUA database.

Supplementary Table 3: SARS-CoV-2 POC IVDs that have received EUA, grouped by their authorized setting (Figure 4B)

Test Type	Authorized Setting	Test Name
Nucleic Acid	CLIA waived laboratories (POC)	Visby Medical COVID-19 Point of care Test
		Mesa Biotech Accula SARS-CoV-2 Test
		Cepheid Xpert Xpress SARS-CoV-2/Flu/RSV
		Cepheid Xpert Xpress SARS-CoV-2/Flu/RSV plus
		Cepheid Xpert Xpress SARS-CoV-2 test
		Cepheid Xpert Omni SARS-CoV-2
		Cepheid Xpert Xpress SARS-CoV-2 DoD
		BioFire Respiratory Panel 2.1-EZ (RP2.1-EZ)
		Roche cobas SARS-CoV-2 & Influenza A/B Nucleic Acid Test for use on the cobas Liat System
		Roche cobas SARS-CoV-2 Nucleic Acid Test for use on the cobas Liat System
		Abbott ID Now COVID-19
	Home/OTC	Lucira CHECK-IT COVID-19 Test Kit
		Cue Health Cue COVID-19 Test
Antigen	CLIA waived laboratories (POC)	BD Veritor System for Rapid Detection of SARS-CoV-2
		BD Veritor System for Rapid Detection of SARS-CoV-2 & Flu A+B
		LumiraDx SARS-CoV-2 Ag Test
		Luminostics Clip COVID Rapid Antigen Test
		Quidel Sofia SARS Antigen FIA
		Quidel Sofia 2 Flu + SARS Antigen FIA
		Access Bio CareStart COVID-19 Antigen test
		Princeton BioMeditech Status COVID-19/Flu
		Celltrion DiaTrust COVID-19 Ag Rapid Test
		Salofa Oy Sienna-Clarity COVID-19 Antigen Rapid Test Cassette
		InBios SCoV-2 Ag Detect Rapid Test
		Ellume Lab COVID Antigen Test
		GenBody COVID-19 Ag Test
		PHASE Scientific INDICAID COVID-19 Rapid Antigen Test
	Home/OTC	Quidel QuickVue At-Home OTC COVID-19 Test
		Ellume COVID-19 Home Test
		Abbott BinaxNOW COVID-19 Ag Card Home Test
		BD Veritor At-Home COVID-19 Test
		Access Bio CareStart COVID-19 Antigen Home Test
		Orasure InteliSwab COVID-19 Rapid Test
Antibody	CLIA waived laboratories (POC)	Nirmidas Biotech MidaSpot COVID-19 Antibody Combo Detection Kit
		ADVAITE RapCov Rapid COVID-19 Test
		Salofa Oy Sienna-Clarity COVIBLOCK COVID-19 IgG/IgM Rapid Test Cassette
		Hangzhou Biotest Biotech RightSign COVID-19 IgG/IgM Rapid Test Cassette

		Assure Tech Assure COVID-19 IgG/IgM Rapid Test Device
		Sugentech SGTi-flex COVID-19 IgG
		Megna Health Rapid COVID-19 IgM/IgG Combo Test Kit
		NOWDiagnostics ADEXUSDx COVID-19 Test
		InBios SCov-2 Detect IgG Rapid Test
		Access Bio CareStart COVID-19 IgM/IgG
		Diabetomics CovAb SARS-CoV-2 Ab Test
		LumiraDx SARS-CoV-2 Ab Test
		Access Bio CareStart EZ COVID-19 IgM/IgG

Supplementary Table 4: POC IVD platforms that have received EUA for a SARS-CoV-2 test, grouped by their most appropriate use case (Figure 7)

Assay Type	Use Case	Company Name/POC Platform
Nucleic Acid	Premium Clinic	Biofire FilmArray 2.1
		Roche cobas Liat
	Premium/Economy Clinic	Cepheid GeneXpert*
	Economy Clinic	Cepheid GeneXpert Omni
		Mesa Biotech Accula
		Abbott ID NOW
	Premium Field	Visby Medical
		Cue Health
		Lucira Health
Antigen	Economy Clinic	LumiraDx
		BD Veritor Plus
		Quidel Sofia 2
		Qorvo Biotechnologies Omnia
		Celltrion Sampinute
		Ellume Lab
	Premium Field	Ellume
		Luminostics Clip
	Economy Field	Abbott BinaxNOW
		Quidel QuickVue
		Salofa Oy
		Celltrion Diatrust
		InBios International
		Princeton Biomeditech
		Access Bio CareStart
		BD Veritor At Home
		Orasure InteliSwab
		Genbody
		Phase Scientific INDICAID
Antibody	Economy Clinic	QIAGEN QIAreach
		LumiraDx
	Economy Field	NOWDiagnostics ADEXUSDx
		ADVAITE RapCoV
		Sugentech SGTI-flex
		Megna Health
		Access Bio CareStart
		Nirmidas Biotech
		Beijing Wantai Biological Pharmacy Enterprise Co. WANTAI
		Salofa Ou Sienna-Clarity
		Hangzhou Biotest Biotech Co. RightSign
		ACON Laboratories
		Hangzhou Laihe Biotech Co. LYHER
		Innovita
		Jiangsu Well Biotech Co. Orawell

		Xiamen Biotime Biotechnology Co., BIOTIME
		Biohit Healthcare
		Assure Tech
		TBG Biotechnology Corp.
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